SUPPLEMENT 152 — APRIL 1991
Volume 100, Number 4, Part 2

12/11/92

CUK-HC3532-25-P024170X

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DAVID H. HUSSEY, MD
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ANNALS
OF OTOLOGY,
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# HEAD AND NECK CANCER: AN ANALYSIS OF THE INCIDENCE, PATTERNS OF TREATMENT, AND SURVIVAL AT THE UNIVERSITY OF IOWA

DAVID H. HUSSEY, MD
IOWA CITY, IOWA

HOWARD B. LATOURETTE, MD
IOWA CITY, IOWA

WILLIAM R. PANJE, MD
CHICAGO, ILLINOIS

A retrospective study was performed with use of tumor registry data to evaluate tumor population characteristics, the patterns of care, and patient survival in 4,506 patients with head and neck cancers seen at The University of Iowa Hospitals and Clinics between 1960 and 1985. The total number of patients with head and neck cancers seen per year and the distribution by anatomic site remained relatively stable over the 26-year period. However, there was a general trend toward more advanced stages in later years. The selection of a treatment modality for this patient population correlated well with the site and stage of the disease and with the treatment philosophy of the managing physicians. Patient survival rates correlated well with the site and stage of the disease. There was a gradual improvement in 5-year survival rates over the 26-year period, from approximately 39% in 1960 to approximately 47% in 1984. This was principally due to an improvement in the 5-year survival rate for patients with "regional stage" disease, from approximately 22% in 1960 to approximately 41% in 1985.

KEY WORDS — head and neck cancer, incidence, patterns of treatment, survival.

Head and neck cancer constitutes 9% of all cancers in the United States and accounts for approximately 4% of all cancer deaths. The annual incidence is 1 to 2 cases per 100,000 population per year. Approximately 14,000 patients die of head and neck cancer each year in this country. The incidence of head and neck cancer is directly related to alcohol and tobacco abuse, and the combined effect of these two factors is significantly greater than the sum of each. It occurs more frequently in males than females (5:1 ratio).

Over 95% of head and neck cancers are squamous cell carcinomas, the principal exception being tumors of the salivary glands. Salivary gland tumors include pleomorphic adenomas, acinic cell tumors, mucoepidermoid carcinomas, adenoid cystic carcinomas, and adenocarcinomas. Other histologic categories that occasionally pertain to the head and neck include sarcomas, melanomas, plasmacytomas, and lymphomas.

Head and neck cancer can be a highly curable disease, although survival rates are compromised by the age and general condition of the patient population that is prone to develop these tumors. As in many cancers, early diagnosis results in a higher incidence of cure. Cure rates for head and neck cancer range from 10% to 90% nationally, depending on the histopathologic type, the anatomic location, size, local extent, the presence of regional and/or distant metastasis, and the general patient condition. In most institutions, the overall 5-year survival rate is in the range of 40% to 45%. Nationally, in the Surveillance Epidemiology End Results (SEER) program, the relative 5-year survival rates for patients with cancers of the oral cavity and oropharynx are 54% in whites and 31% in blacks.[1] (The SEER program uses relative survival rates, which are defined as the survival rate of a patient cohort relative to the survival rate of a similar group from the general population. This is different from the survival rates for Iowa patients in this document. The survival rates in this document are absolute survival rates computed by the life table method.)

Both surgery and radiotherapy play a major role in the management of head and neck cancers, and improvements in these techniques have extended the potential for cure. Prior to 1960, most patients with head and neck cancers were treated with a single modality, either surgery or radiotherapy. However, many of the patients who were treated with a single modality for advanced cancers died of uncontrolled disease at the primary site and/or the regional lymph nodes. As a result, treatment patterns have gradually shifted toward combined modalities of treatment for patients with advanced disease.

At one time, distant metastasis from squamous carcinomas of the head and neck was thought to be very rare. As control rates above the clavicles improved, the incidence of overt distant metastasis increased. In the past, chemotherapy has played a lesser role in the management of cancers of the head and neck than has surgery or radiotherapy, although it has been used more frequently in recent years as an adjunctive treatment for patients with a high risk of

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From the Division of Radiation Oncology, Department of Radiology, The University of Iowa College of Medicine, Iowa City, Iowa (Hussey, Latourette). Dr Panje is now at the Department of Otolaryngology–Head and Neck Surgery, University of Chicago, Chicago, Illinois.

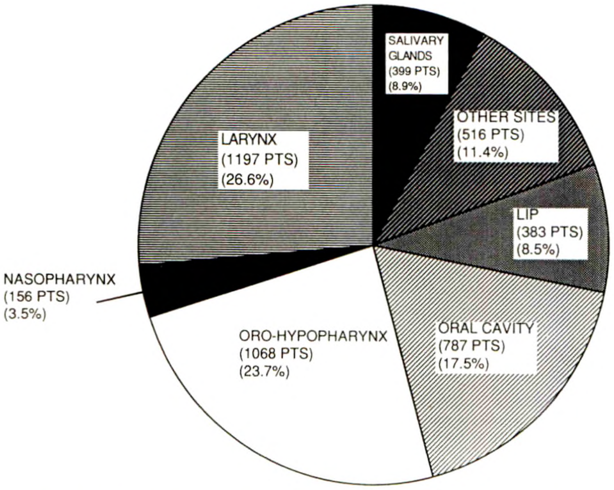

Fig 1. Distribution of head and neck cancers at University of Iowa Hospitals and Clinics by major site, 1960 to 1985.

recurrence or metastasis.

This document is a review of the experience with head and neck cancer at The University of Iowa Hospitals and Clinics (UIHC) between 1960 and 1985. The specific aims of the analysis were 1) to evaluate the site and stage distribution of head and neck cancers at UIHC, 2) to analyze the patterns of care for these patients as a function of site, stage, and year of presentation, and 3) to evaluate patient survival as it relates to site, stage, treatment modality, and year of presentation.

## UNIVERSITY OF IOWA TUMOR REGISTRY

The UIHC Tumor Registry is one of the oldest registries in the nation. It contains data on all patients with malignant tumors and/or some benign neoplasms who have been seen at UIHC between 1938 and the present. The information collected includes patient identifiers, the anatomic site and stage of the disease, histology, treatment information, and follow-up status. The data are collected, recorded, and processed by trained personnel who review the medical records and pertinent departmental records and correspond with the patient, the family, or the family physician. Follow-up information is updated annually from the hospital medical records, patient letters, and telephone calls to referring physicians. Over 103,000 patients were on file at the UIHC Tumor Registry as of January 1990, and only 2% of cases have been lost to follow-up. This superb record reflects the long-standing Iowa tradition of loyal patient participation in follow-up and the geographic stability of the middle-aged and elderly of the state.

When using Tumor Registry data, it is essential to recognize the quality of this information. Some of this information can be quite accurate, some is very helpful, and some has definite limitations. There may be gaps in the information in the hospital record and occasional uncertainties as to the site and stage of the disease. Changes in hospital record-keeping, staging capabilities, and Tumor Registry personnel over the years could lead to variations in the results over time. Furthermore, there are several characteristics of the system that could lead to a bias in results reported with different treatment methods.

One problem is that a relatively crude staging system was employed during the period. Patients were classified as having localized, regional, or distant disease, and within each category the extent of the disease could vary from minimal to massive. It is likely that the patients treated with radiotherapy or combined surgery and radiotherapy in this report had more advanced disease than those treated with surgery alone.

A second problem is that cancers were staged on the basis of either clinical or pathologic findings. Consequently, patients who were treated surgically

Fig 2. Distribution of head and neck cancers at University of Iowa by primary site, 1960 to 1985.

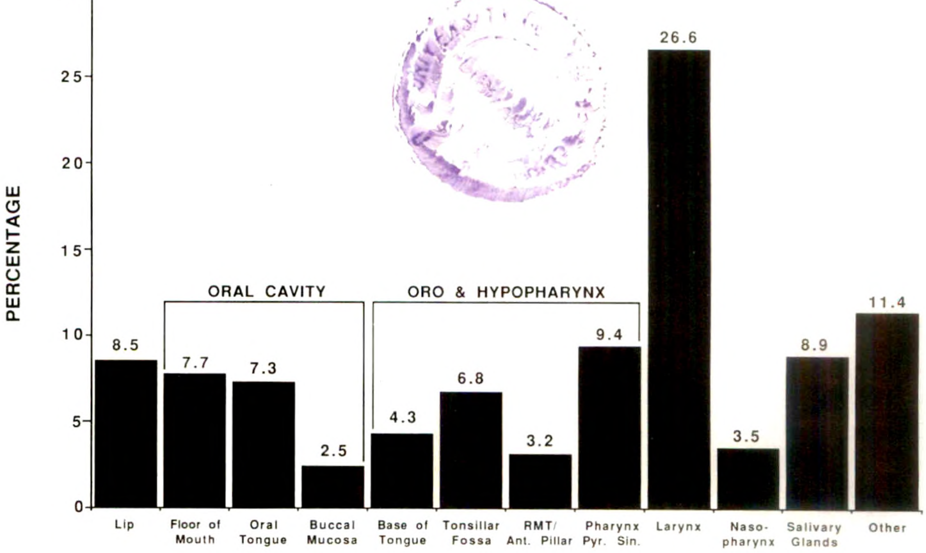

TABLE 1. DISTRIBUTION OF HEAD AND NECK CANCERS AT UNIVERSITY OF IOWA BY SUBSITE AND YEAR OF PRESENTATION

| | *1960-1964* | *1965-1969* | *1970-1974* | *1975-1979* | *1980-1985* | *Uncertain or Multiple Years* | *Total* |
|---|---|---|---|---|---|---|---|
| Lip | 90 | 87 | 69 | 67 | 50 | 20 | 383 |
| Oral cavity | 154 | 161 | 166 | 151 | 135 | 20 | 787 |
| Floor of mouth | 63 | 58 | 81 | 77 | 62 | 7 | 348 |
| Oral tongue | 56 | 75 | 69 | 54 | 62 | 11 | 327 |
| Buccal mucosa | 35 | 28 | 16 | 20 | 11 | 2 | 112 |
| Orohypopharynx | 160 | 213 | 214 | 204 | 252 | 25 | 1,068 |
| Retromolar trigone or anterior tonsillar pillar | 6 | 22 | 33 | 34 | 45 | 6 | 146 |
| Tonsil | 55 | 65 | 58 | 55 | 65 | 10 | 308 |
| Base of tongue | 27 | 37 | 38 | 33 | 54 | 3 | 192 |
| Pharynx or pyriform sinus | 72 | 89 | 85 | 82 | 88 | 6 | 422 |
| Larynx | 218 | 230 | 256 | 213 | 274 | 6 | 1,197 |
| Nasopharynx | 28 | 42 | 25 | 24 | 36 | 1 | 156 |
| Salivary glands | 61 | 87 | 84 | 90 | 68 | 9 | 399 |
| Other | 79 | 94 | 103 | 85 | 118 | 37 | 516 |
| Total | 790 | 914 | 917 | 834 | 933 | 118 | 4,506 |

had additional staging information that was not available for patients treated with radiotherapy or chemotherapy alone. Thus, patients with microscopic metastasis in regional lymph nodes would have been classified as having "regional disease" if treated surgically but as having "localized disease" if treated with radiotherapy only.

A third potential bias results from the way patients from the Veterans Administration Hospital (VAH) are counted. Radiation Oncology at UIHC treats patients from the VAH, and these patients are included in the UIHC Tumor Registry file. However, VAH patients that are treated with surgery alone are not included. This introduces a bias, because VAH patients are more likely to present with advanced cancers than are UIHC patients.

## PATIENT POPULATION

### ANATOMIC SITES

Between 1960 and 1985, 4,506 patients with head and neck cancers were seen at UIHC. For the purpose of this analysis, the tumors were classified as cancers of the lip, oral cavity, orohypopharynx, larynx, nasopharynx, salivary glands, and other head and neck sites. The site distribution is illustrated in Fig 1. Of the total population, 8.5% had cancers of the lip, 17.5% had cancers of the oral cavity, 23.7% had cancers of the oropharynx and hypopharynx, 26.6% had cancers of the larynx, 3.5% had cancers of the nasopharynx, 8.9% had cancers of the salivary glands, and 11.4% had cancers of other sites.

The oral cavity and orohypopharynx have been divided into several subsites, and the patient distribution by subsite is shown in Fig 2. In general, there was little variation in the distribution of the tumors by anatomic site over the duration of the study (Table 1). The total number of head and neck cancers seen each year at UIHC has remained relatively stable at approximately 170 patients per year.

### STAGE

The patients were staged by use of either clinical or pathologic criteria, whichever was available for each individual case. A relatively simple staging system was employed: 1) localized, 2) regional, and 3) distant. If there was no evidence of spread beyond the primary site, the patients were classified as having localized disease. If there was evidence of metastasis to regional lymph nodes but no evidence of hematogenous spread, they were classified as having regional disease. This could be based on either clinically palpable nodes or histologically positive nodes at operation. If distant metastases were evident at the time of initial evaluation, the patients were classified as having distant disease. Of the total population, 40.1% of the patients were classified as having localized tumors, 40.8% as having

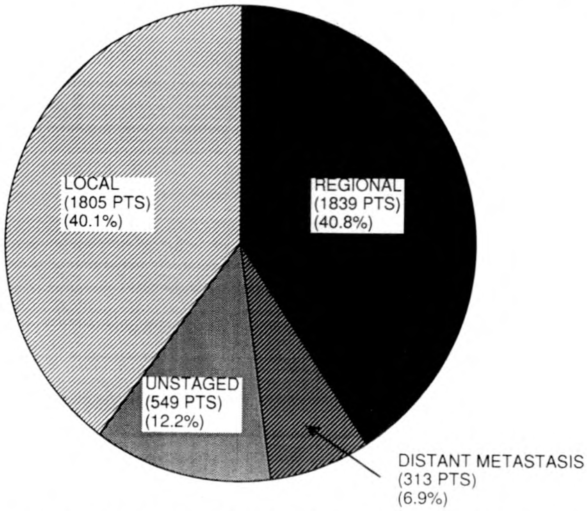

Fig 3. Distribution of head and neck cancers at University of Iowa by clinical stage, 1960 to 1985.

TABLE 2. DISTRIBUTION OF HEAD AND NECK CANCERS AT UNIVERSITY OF IOWA BY SUBSITE, STAGE, AND YEAR OF PRESENTATION

| | *1960-1964* | | | *1965-1969* | | | *1970-1974* | | | *1975-1979* | | | *1980-1985* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Site* | *L* | *R* | *D* | *L* | *R* | *D* | *L* | *R* | *D* | *L* | *R* | *D* | *L* | *R* | *D* |
| Lip | 67 | 11 | 0 | 70 | 4 | 0 | 45 | 6 | 1 | 37 | 15 | 1 | 42 | 4 | 1 |
| | 86% | 14% | | 95% | 5% | | 87% | 11% | 2% | 70% | 28% | 2% | 89% | 9% | 2% |
| Oral cavity | 73 | 62 | 8 | 61 | 77 | 4 | 67 | 77 | 7 | 51 | 77 | 2 | 52 | 66 | 7 |
| | 51% | 43% | 6% | 43% | 54% | 3% | 44% | 51% | 5% | 39% | 59% | 2% | 42% | 53% | 5% |
| Floor of mouth | 22 | 29 | 3 | 14 | 34 | 2 | 26 | 46 | 2 | 17 | 48 | 0 | 22 | 32 | 3 |
| Oral tongue | 30 | 23 | 1 | 35 | 34 | 0 | 34 | 24 | 5 | 25 | 21 | 2 | 25 | 29 | 3 |
| Buccal mucosa | 21 | 10 | 4 | 12 | 9 | 2 | 7 | 7 | 0 | 9 | 8 | 0 | 5 | 5 | 1 |
| Orohypopharynx | 44 | 102 | 5 | 28 | 137 | 22 | 34 | 131 | 35 | 37 | 116 | 35 | 42 | 151 | 40 |
| | 29% | 68% | 3% | 15% | 73% | 12% | 12% | 69% | 19% | 20% | 62% | 19% | 18% | 65% | 12% |
| RT or ATP | 2 | 3 | 0 | 8 | 11 | 1 | 10 | 13 | 10 | 9 | 14 | 8 | 10 | 24 | 6 |
| Tonsil | 16 | 33 | 3 | 10 | 40 | 5 | 8 | 42 | 6 | 9 | 34 | 9 | 9 | 43 | 7 |
| Base of tongue | 9 | 16 | 0 | 2 | 23 | 4 | 5 | 26 | 4 | 6 | 20 | 5 | 8 | 36 | 9 |
| Pharynx or PS | 17 | 50 | 2 | 8 | 63 | 12 | 11 | 50 | 15 | 13 | 48 | 13 | 15 | 48 | 18 |
| Larynx | 139 | 60 | 10 | 143 | 66 | 5 | 124 | 93 | 18 | 101 | 67 | 14 | 100 | 119 | 14 |
| | 66% | 29% | 5% | 67% | 31% | 2% | 53% | 39% | 8% | 55% | 37% | 8% | 43% | 51% | 6% |
| Nasopharynx | 5 | 18 | 4 | 8 | 19 | 5 | 4 | 10 | 4 | 7 | 12 | 5 | 7 | 18 | 5 |
| | 18% | 67% | 15% | 25% | 59% | 16% | 22% | 56% | 22% | 29% | 50% | 21% | 23% | 60% | 17% |
| Salivary glands | 42 | 11 | 3 | 56 | 14 | 6 | 53 | 16 | 2 | 37 | 13 | 4 | 40 | 8 | 2 |
| | 75% | 20% | 5% | 74% | 18% | 8% | 75% | 22% | 3% | 69% | 24% | 7% | 80% | 16% | 4% |
| Other | 36 | 33 | 7 | 27 | 49 | 2 | 42 | 49 | 11 | 19 | 47 | 12 | 34 | 48 | 15 |
| | 47% | 43% | 9% | 35% | 63% | 2% | 41% | 48% | 11% | 25% | 60% | 15% | 35% | 49% | 16% |
| Total | 406 | 297 | 37 | 393 | 366 | 44 | 369 | 382 | 78 | 289 | 347 | 73 | 317 | 414 | 84* |
| | 54.9% | 40.1% | 5.0% | 48.9% | 45.6% | 5.5% | 44.5% | 46.1% | 9.4% | 40.8% | 48.9% | 10.2% | 38.9% | 50.8% | 10.3% |

Excludes unstaged patients.

L — localized, R — regional, D — distant, RT — retromolar trigone, ATP — anterior tonsillar pillar, PS — pyriform sinus.

*Indicates patients accrued during 6-year period.

regional tumors, and 6.9% as having distant metastasis (Fig 3). Approximately 12% of the total population was not staged.

Although the number of head and neck cancer patients referred to UIHC remained stable over the years, there was a gradual shift toward more advanced stages (Table 2). In the early 1960s, 54.9% of the patients were classified as having localized disease because the tumor appeared to be confined to the primary site. The percentage of patients staged as localized gradually decreased to 38.9% in the early 1980s. During the same time, the percentage of patients classified as having regional metastasis increased from 40.1% to 50.8%. Although some of this difference may be attributable to improvements in staging technique (ie, stage migration), it is thought to be mainly due to a change in the pattern of referral. Over the years, there has been a trend toward more advanced cases being referred to UIHC and less advanced cases being treated locally.

## PATTERNS OF TREATMENT

Almost all of the patients in this series were treated with either surgery or radiotherapy (Fig 4). For the purposes of this analysis, surgery refers to some form of resection, not simply a biopsy. Relatively few patients in this series received chemotherapy as part of the initial course of treatment.

Surgery was the most commonly employed treatment modality. It was used in the initial course of treatment in 57.5% (2,590 patients) of the patients. Approximately 35% (1,576 patients) were treated with surgery alone, and 21.7% (977 patients) were treated with combined surgery and radiotherapy. A small number of patients were treated with surgery and chemotherapy (0.2%; 10 patients) or with all three modalities (0.6%; 27 patients).

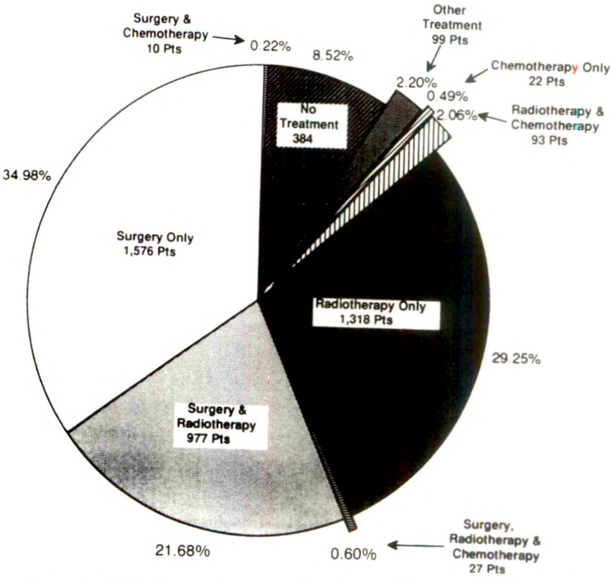

Fig 4. Initial treatment methods for total population of 4,506 patients with head and neck cancer, 1960 to 1985.

TABLE 3. COMPARISON OF USE OF SURGERY ALONE, RADIOTHERAPY ALONE, AND COMBINED SURGERY AND RADIOTHERAPY AS FUNCTION OF YEAR OF DIAGNOSIS (1960 TO 1985)

| *Years* | *Surgery Alone* | *Radiotherapy Alone* | *Combined Surgery and Radiotherapy* |
|---|---|---|---|
| 1960-1964 | 33.9% | 44.2% | 15.4% |
| 1965-1969 | 43.3% | 29.2% | 22.2% |
| 1970-1974 | 28.7% | 36.6% | 25.0% |
| 1975-1979 | 35.6% | 25.4% | 26.7% |
| 1980-1985* | 36.7% | 25.3% | 24.1% |

Small number of patients in each therapeutic group also received chemotherapy (<5%).

*Includes patients accrued over 6-year interval.

Radiotherapy was the second most commonly used treatment modality in this series of patients. Of the total population, 53.6% (2,415 patients) received radiotherapy as part of their initial treatment. This included 29.2% (1,318 patients) who were treated with radiotherapy alone, 21.7% (977 patients) who were treated with surgery and radiotherapy, 2.1% (93 patients) who were treated with radiotherapy and chemotherapy, and 0.6% (27 patients) who were treated with all three modalities.

Only 3.4% (152 patients) of the head and neck cancer population received chemotherapy as part of their initial management, and the majority of these patients also received radiotherapy. A small number (2.2%; 99 patients) were listed as having other treatments, and 8.5% (384 patients) received no therapy (Fig 4). The patients listed as having other treatments were those who were seen initially at UIHC but were referred elsewhere for treatment.

## TREATMENT SELECTION

The selection of a treatment modality for head and neck cancer patients varied with the year of presentation. Combined modality therapy was rarely employed prior to 1964. Most of the patients in that era were treated with radiotherapy or surgery alone. In 1964 to 1965, the use of combined surgery and radiotherapy increased to approximately 25% of the head and neck cancer population, and the percentage of patients treated with combined modality therapy has remained relatively constant since that time (Table 3).

The proportion of patients treated with surgery alone or radiotherapy alone varied in a reciprocal fashion throughout the years (Table 3). During two periods, in the early 1960s and the early 1970s, a greater number of patients were treated with radiotherapy alone. On the other hand, a greater percentage were treated with surgery alone during the late 1960s, late 1970s, and early 1980s. In recent years, approximately 35% of patients have been treated with surgery alone, 25% with radiotherapy alone, and 25% with combined surgery and radiotherapy. Only 3% to 5% of the patients in this series were treated with chemotherapy, and the percentage remained relatively constant over the 26-year span of this study (Table 4). Approximately 10% received no treatment or were referred elsewhere for therapy.

TABLE 4. DISTRIBUTION BY TREATMENT MODALITY AND YEAR OF PRESENTATION

| *Year* | *Surgery ±OT* | *Radiotherapy ±OT* | *Chemotherapy ±OT* |
|---|---|---|---|
| 1960 | 55 | 78 | 0 |
| 1961 | 69 | 97 | 3 |
| 1962 | 71 | 92 | 20 |
| 1963 | 86 | 110 | 23 |
| 1964 | 108 | 94 | 11 |
| 1965 | 133 | 95 | 8 |
| 1966 | 129 | 84 | 1 |
| 1967 | 120 | 90 | 2 |
| 1968 | 114 | 100 | 13 |
| 1969 | 103 | 101 | 12 |
| 1970 | 116 | 106 | 3 |
| 1971 | 108 | 121 | 3 |
| 1972 | 88 | 124 | 1 |
| 1973 | 92 | 105 | 3 |
| 1974 | 98 | 99 | 4 |
| 1975 | 92 | 97 | 2 |
| 1976 | 116 | 100 | 3 |
| 1977 | 90 | 66 | 1 |
| 1978 | 107 | 79 | 0 |
| 1979 | 119 | 93 | 2 |
| 1980 | 97 | 79 | 0 |
| 1981 | 113 | 85 | 1 |
| 1982 | 89 | 76 | 5 |
| 1983 | 91 | 66 | 12 |
| 1984 | 85 | 76 | 1 |
| 1985 | 92 | 79 | 11 |

Data are numbers of patients. Excludes patients treated in uncertain or multiple years.

±OT — with or without other treatment.

## FACTORS INFLUENCING SELECTION OF TREATMENT MODALITY

A variety of factors could have influenced the selection of a treatment modality for this patient population. These included 1) tumor and patient characteristics, eg, the site and stage of the disease and the general condition of the patient; 2) the treatment philosophy of the managing physician, ie, the surgical oncologist, radiation oncologist, or medical oncologist; and 3) the availability of specialized radiotherapy equipment, surgical techniques, or chemotherapeutic agents.

*Tumor Site.* The selection of a treatment modality correlated well with the site of the primary tumor (Figs 5-7). As expected, the majority of patients with lip cancers were treated surgically. However, more patients with lip cancer were treated with radiotherapy alone than with combined surgery and radiotherapy (Fig 5).

The majority of the patients with oral cavity tumors were treated with surgery, either alone or in combination with other treatment. Cancers of the oropharynx and hypopharynx, on the other hand, were more frequently managed by radiotherapy or

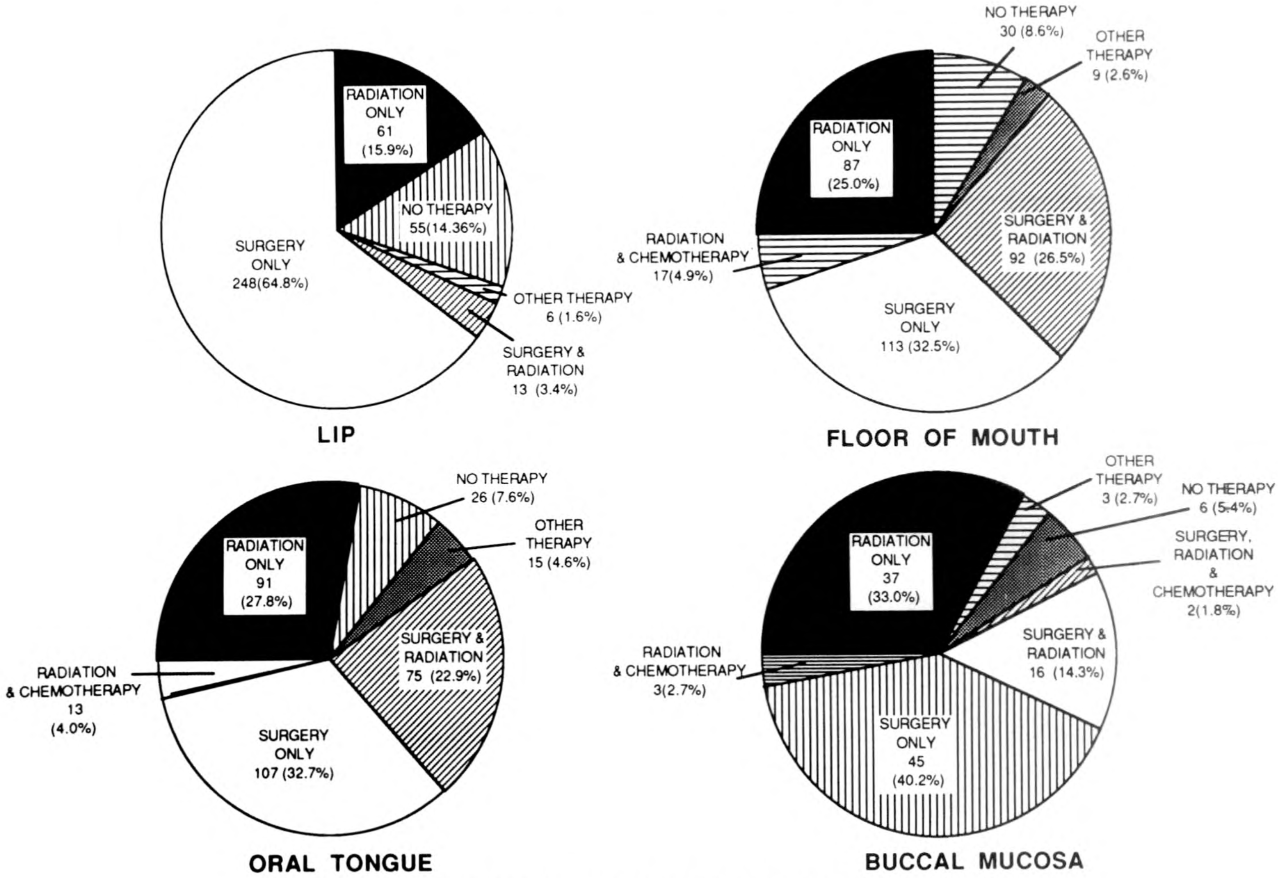

Fig 5. University of Iowa initial treatment methods for oral cavity and lip cancers.

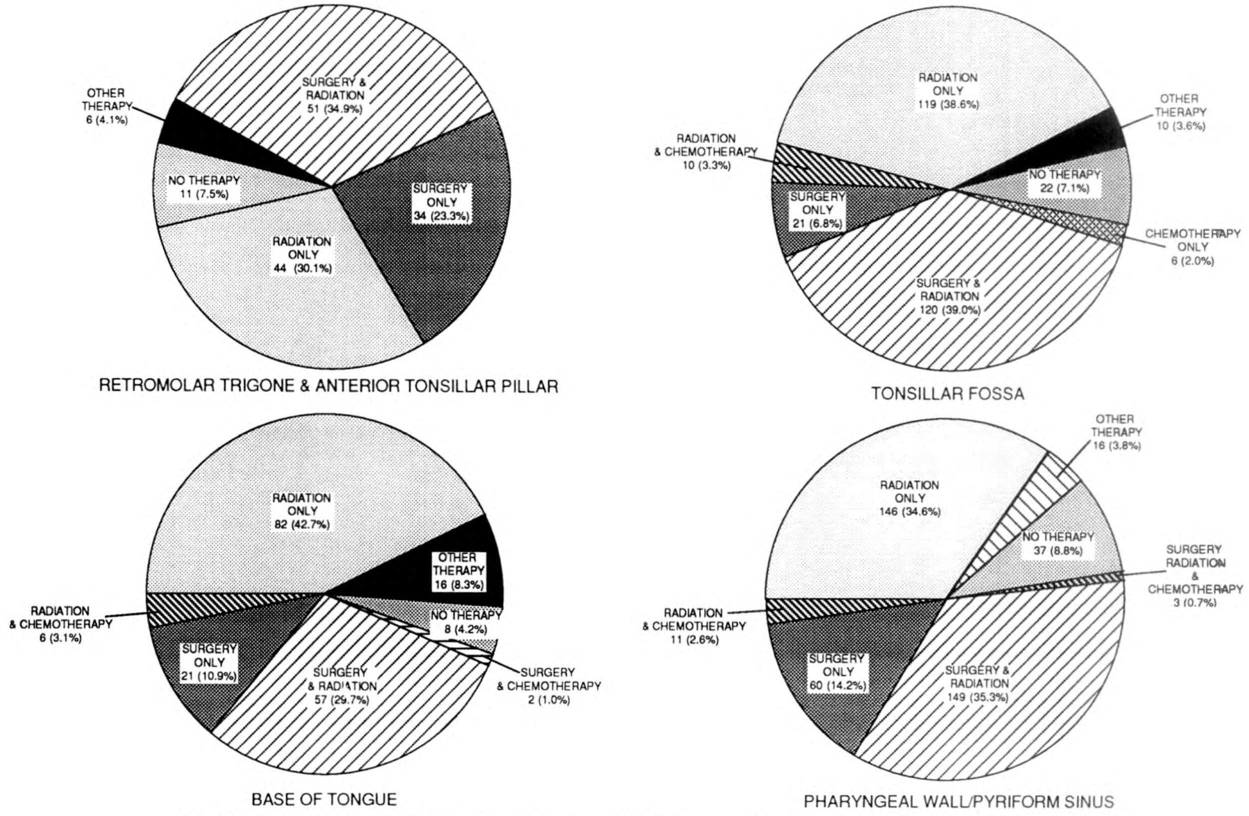

Fig 6. University of Iowa initial treatment methods for oropharynx and hypopharynx cancers.

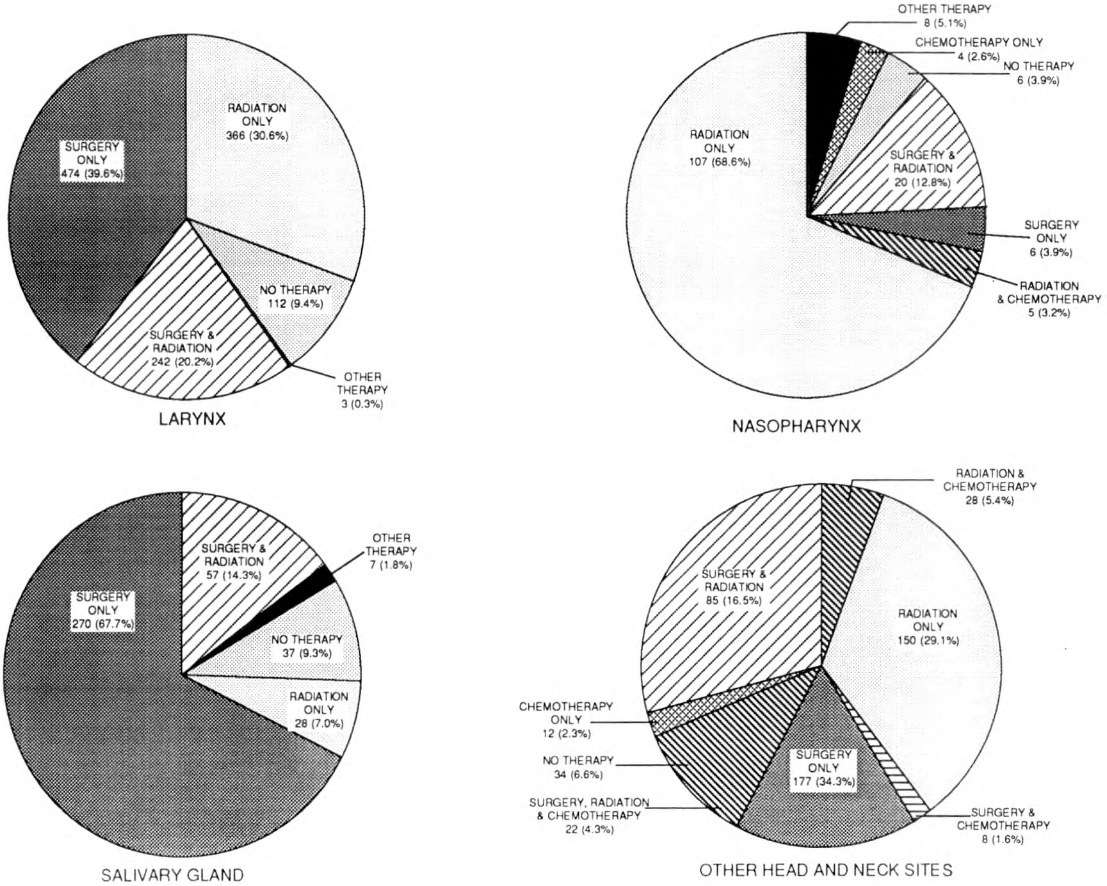

Fig 7. University of Iowa initial treatment methods for cancers of larynx, nasopharynx, salivary glands, and other sites.

combined therapy (Fig 6). This was because tumors of the oropharynx and hypopharynx are less accessible to complete excision without functional impairment, and there is a greater risk of lymph node metastasis with tumors of these sites. A somewhat greater percentage of patients with retromolar trigone or anterior tonsillar pillar cancers were treated with surgery alone, usually because these tumors are more amenable to surgical treatment by composite resection.

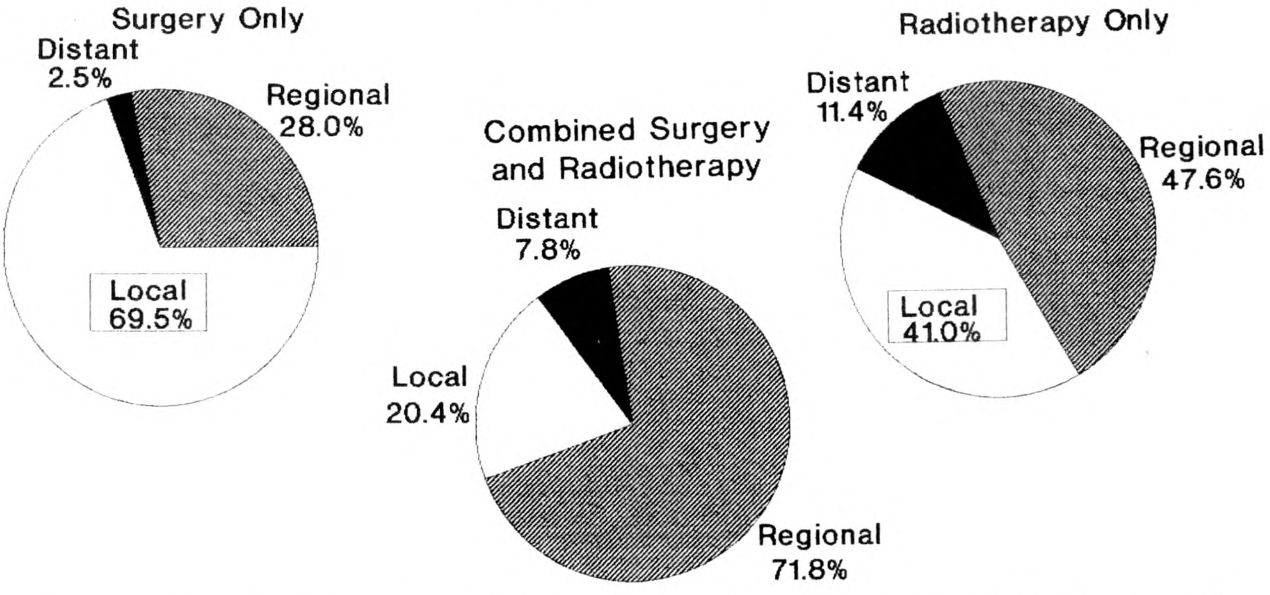

Fig 8. Comparison of stage distribution for patients treated with surgery only, radiotherapy only, and combined surgery and radiotherapy, 1960 to 1985.

TABLE 5. STAGE DISTRIBUTION FOR HEAD AND NECK CANCER PATIENTS TREATED WITH VARIOUS MODALITIES (1960 TO 1985)

| *Treatment Methods* | *Clinical Stage* | | | *Unstaged Patients* |
|---|---|---|---|---|
| | *Localized* | *Regional* | *Distant* | |
| Surgery only | 69.5%<br>(973/1,400) | 28.0%<br>(392/1,400) | 2.5%<br>(35/1,400) | 176 |
| Radiotherapy only | 41.0%<br>(494/1,204) | 47.6%<br>(573/1,204) | 11.4%<br>(137/1,204) | 114 |
| Surgery and radiotherapy | 20.4%<br>(189/927) | 71.8%<br>(666/927) | 7.8%<br>(72/927) | 50 |
| Chemotherapy only | 14.3%<br>(2/14) | 64.3%<br>(9/14) | 21.4%<br>(3/14) | 8 |
| Surgery and chemotherapy | 12.5%<br>(1/8) | 37.5%<br>(3/8) | 50.0%<br>(4/8) | 2 |
| Radiotherapy and chemotherapy | 20.0%<br>(16/80) | 58.8%<br>(47/80) | 21.3%<br>(17/80) | 13 |
| Surgery, radiotherapy, and chemotherapy | 16.0%<br>(4/25) | 76.0%<br>(19/25) | 8.0%<br>(2/25) | 2 |
| Other treatment | 24.4%<br>(22/90) | 54.4%<br>(49/90) | 21.1%<br>(19/90) | 9 |
| No treatment | 49.8%<br>(104/209) | 38.8%<br>(81/209) | 11.5%<br>(24/209) | 175 |
| Total | 45.8%<br>(1,805/3,957) | 46.7%<br>(1,839/3,957) | 7.9%<br>(313/3,957) | |

For the purpose of this analysis, cancers of the larynx included tumors of the supraglottic larynx (epiglottis, aryepiglottic folds, false vocal folds, and arytenoids), glottis, and subglottic larynx. During this period, 39.6% of the patients with cancers of the larynx were treated with surgery alone, 30% with radiotherapy alone, and 20.2% with combined surgery and radiotherapy (Fig 7). The choice of a treatment modality for these patients was determined principally by location and extent of the tumor.

Almost all of the patients with nasopharyngeal cancers were treated with radiotherapy (Fig 7). Ra-

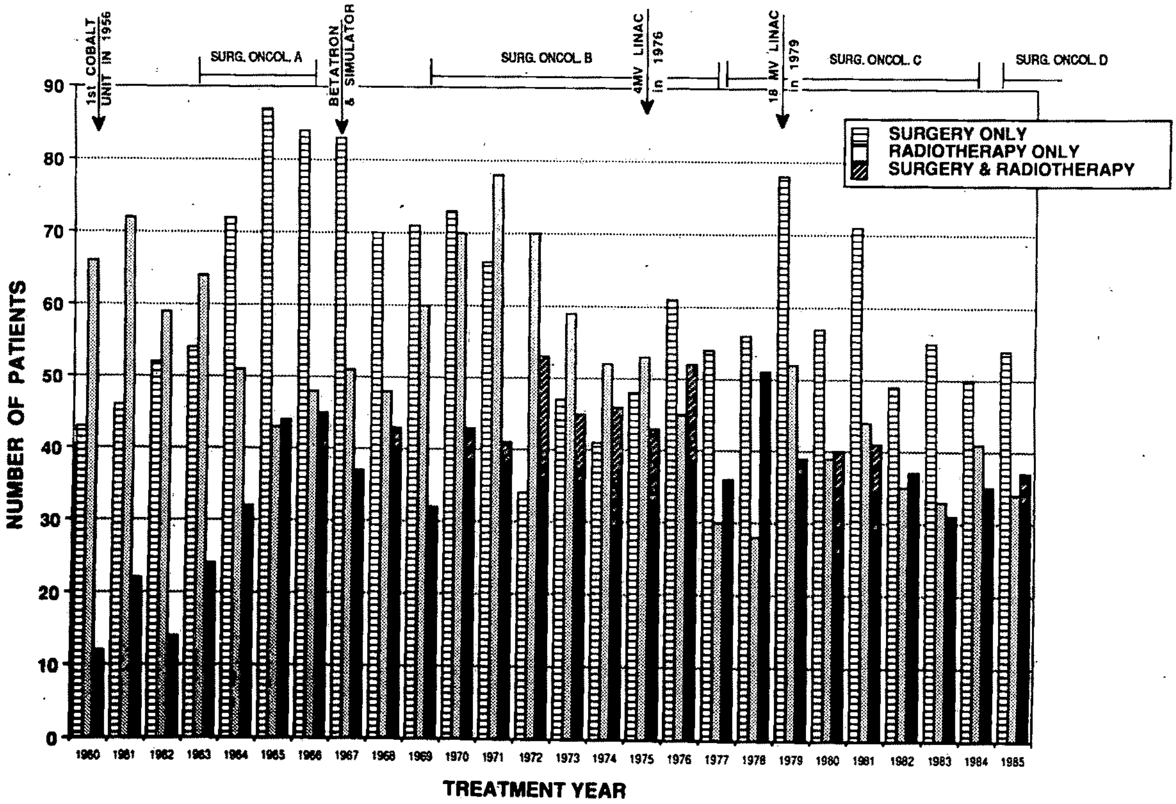

Fig 9. University of Iowa treatment methods as function of year of treatment.

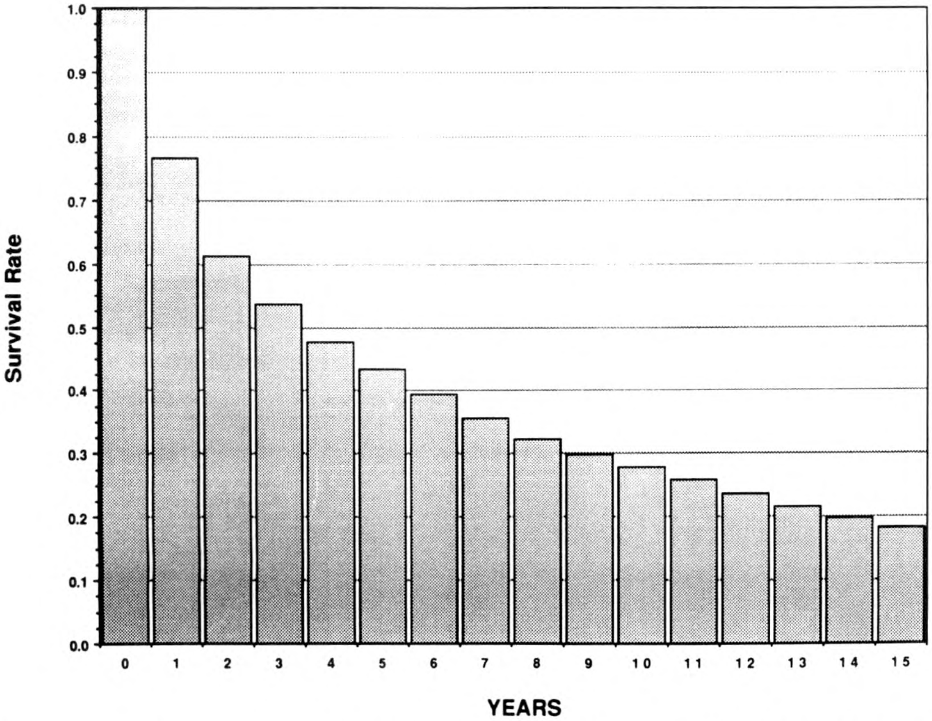

Fig 10. Actuarial survival for total population of 4,506 patients with head and neck cancer, 1960 to 1985.

diotherapy alone was used in the treatment of 68.6% of the patients with nasopharyngeal cancers. Only 4% were treated with surgery only and 12.8% with a combination of surgery and irradiation.

The majority of patients with salivary gland tumors, on the other hand, were treated with surgery (Fig 7). Two thirds of these patients were treated with surgery alone. Many of these patients had benign mixed tumors. Only 14.3% of the patients with salivary gland tumors were treated with combined surgery and radiotherapy. These were mainly malignant salivary gland tumors with poor prognostic features.

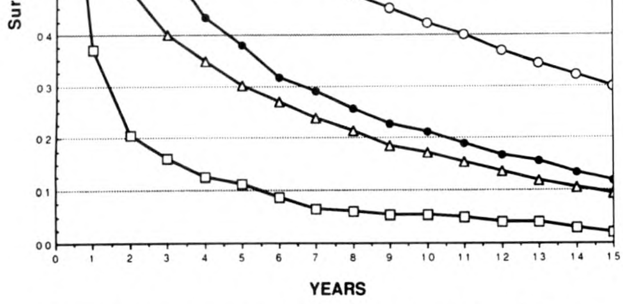

Fig 11. Actuarial survival by stage of disease for 4,506 patients with head and neck cancer, 1960 to 1985.

*Tumor Stage.* Tumor extent was one of the principal factors determining the selection of a treatment modality. Patients with small tumors limited to the primary site were frequently treated with surgery only. Patients with locally advanced disease, on the other hand, were often treated with radiotherapy or combined modality therapy, and patients with hematogenous metastases were often treated with chemotherapy or combined chemotherapy and radiotherapy. It was not surprising that the stage distribution differed considerably for the groups treated with various modalities.

Over two thirds (69.5%) of the patients treated with surgery only were classified as having disease limited to the primary site, and 28% had regional lymph node metastasis. In contrast, only 20.4% in the group treated with combined surgery and radiotherapy had disease confined to the primary site,

TABLE 6. COMPARISON OF 2-, 5-, AND 10-YEAR SURVIVAL RATES BY TUMOR SITE (ALL TREATMENT GROUPS, 1960 TO 1985)

| *Site* | *No. of Patients* | *2-Year Survival* | *5-Year Survival* | *10-Year Survival* |
|---|---|---|---|---|
| Lip | 383 | 82.2% | 61.2% | 37.2% |
| Floor of mouth | 348 | 56.5% | 37.2% | 22.6% |
| Oral tongue | 327 | 58.4% | 40.2% | 23.3% |
| Buccal mucosa | 112 | 56.3% | 43.2% | 21.9% |
| Retromolar trigone or anterior tonsillar pillar | 146 | 54.6% | 38.5% | 25.6% |
| Tonsillar fossa | 308 | 50.8% | 32.6% | 20.1% |
| Base of tongue | 192 | 41.1% | 25.3% | 13.9% |
| Pharynx or pyriform sinus | 422 | 36.2% | 18.5% | 8.8% |
| Larynx | 1,197 | 71.1% | 50.8% | 32.3% |
| Salivary glands | 399 | 83.1% | 71.2% | 60.5% |

Depicts actuarial survival (life table).

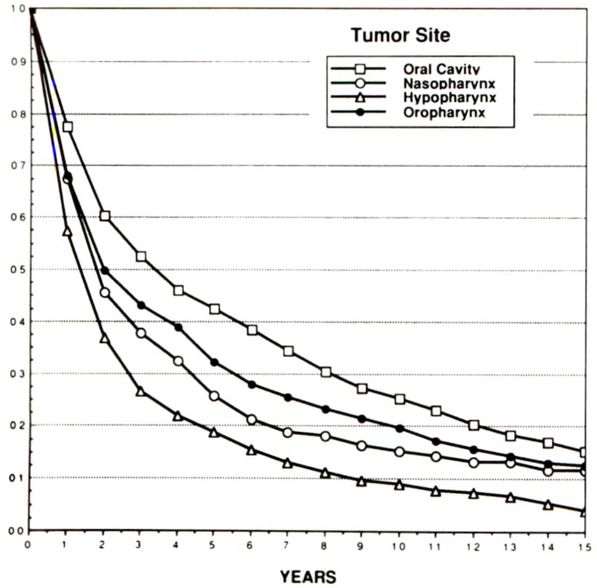

Fig 12. Actuarial survival curves for cancers (all stages) of oral cavity, oropharynx, hypopharynx, and nasopharynx, 1960 to 1985.

and 71.8% had regional lymph node metastasis. This was because patients who were found to have regional lymph node metastasis at operation were usually referred for postoperative radiotherapy. Approximately half (47.6%) of the patients treated with radiotherapy only were classified as having regional lymph node metastasis, although a significant number of the patients listed as having localized disease would have been found to have regional metastasis had they been surgically staged (Fig 8 and Table 5).

The difference in the extent of the disease in these treatment groups was even greater than these numbers would suggest. First, the stage categories were broad, and the more advanced cases within each stage were more likely to be treated with radiotherapy or combined modality therapy than with surgery. Furthermore, there was an inherent staging bias because staging was done on the basis of either clinical or histopathologic information. Patients who were treated with surgery and found to have microscopic metastasis in regional lymph nodes were classified as having regional disease. Similar patients treated with radiotherapy alone would have been classified as having localized disease, because this information would not have been available.

*Surgical Oncologists*. Head and neck tumors were managed by four different surgical oncologists during this 26-year period (Fig 9). Surgical oncologist A was in charge of the head and neck oncology program between 1963 and 1966, and surgical oncologist B directed the program between 1969 and 1977. Surgical oncologist C was in charge of head and neck tumors between 1977 and 1984. A fourth surgical oncologist came in 1985, the final year of the study. Prior to 1963, and between 1966 and 1969, no specific surgical oncologist was designated, and patients were managed by all of the faculty in the otolaryngology department.

The pattern of management for the head and neck population correlated well with the appointments of the various surgical oncologists (Fig 9). Prior to the appointment of surgical oncologist A, the majority of patients were treated with a single modality — approximately 45% were treated with radiotherapy alone, and 30% to 35% with surgery alone. Only about 10% of the patients in this era were treated with combined surgery and radiotherapy. With the appointment of surgical oncologist A, the use of combined therapy increased to approximately 25%. During the tenure of surgical oncologist A, the use of radiotherapy alone decreased from approximately 45% to approximately 30%, and the use of surgery alone increased from 30% to 35% to 40% to 45%.

During the tenure of surgical oncologist B, more patients were treated with radiotherapy or combined radiotherapy and surgery. Surgery as the sole treatment modality was employed less frequently. During this period, approximately 35% of the patients were treated with radiotherapy alone, 30% with surgery alone, and 25% with combined surgery and radiotherapy.

During the tenure of surgical oncologist C, there was a slight shift toward surgical management. During this time, approximately 35% were treated with surgery only, approximately 25% with radiotherapy only, and approximately 25% with surgery and radiotherapy (Fig 9).

*Radiation Oncologists and Radiotherapy Facilities*. Throughout this period, radiotherapy for head and neck cancer was directed by one radiation oncologist, so that this was not a variable. However, the radiotherapy facility was expanded several

TABLE 7. COMPARISON OF SURVIVAL RATES BY SITE AND STAGE FOR PATIENTS WITH ORAL CAVITY, OROPHARYNGEAL, HYPOPHARYNGEAL, AND NASOPHARYNGEAL PRIMARY SITES (1960 TO 1985)

| | *2-Year Survival* | | | *5-Year Survival* | | |
|---|---|---|---|---|---|---|
| *Primary Site* | *Localized (T1-4N0M0)* | *Regional (T1-4N1-3M0)* | *Distant (T1-4N0-3M1)* | *Localized (T1-4N0M0)* | *Regional (T1-4N1-3M0)* | *Distant (T1-4N0-3M1)* |
| Oral cavity | 75.6% | 46.9% | 23.2% | 58.5% | 30.6% | 13.0% |
| Oropharynx | 74.0% | 50.2% | 11.1% | 49.4% | 31.7% | 11.1% |
| Hypopharynx | 55.6% | 34.7% | 21.7% | 33.1% | 17.2% | 6.4% |
| Nasopharynx | 64.5% | 49.4% | 25.0% | 38.5% | 28.9% | 8.3% |

Uses life table survival method and excludes unstaged patients.

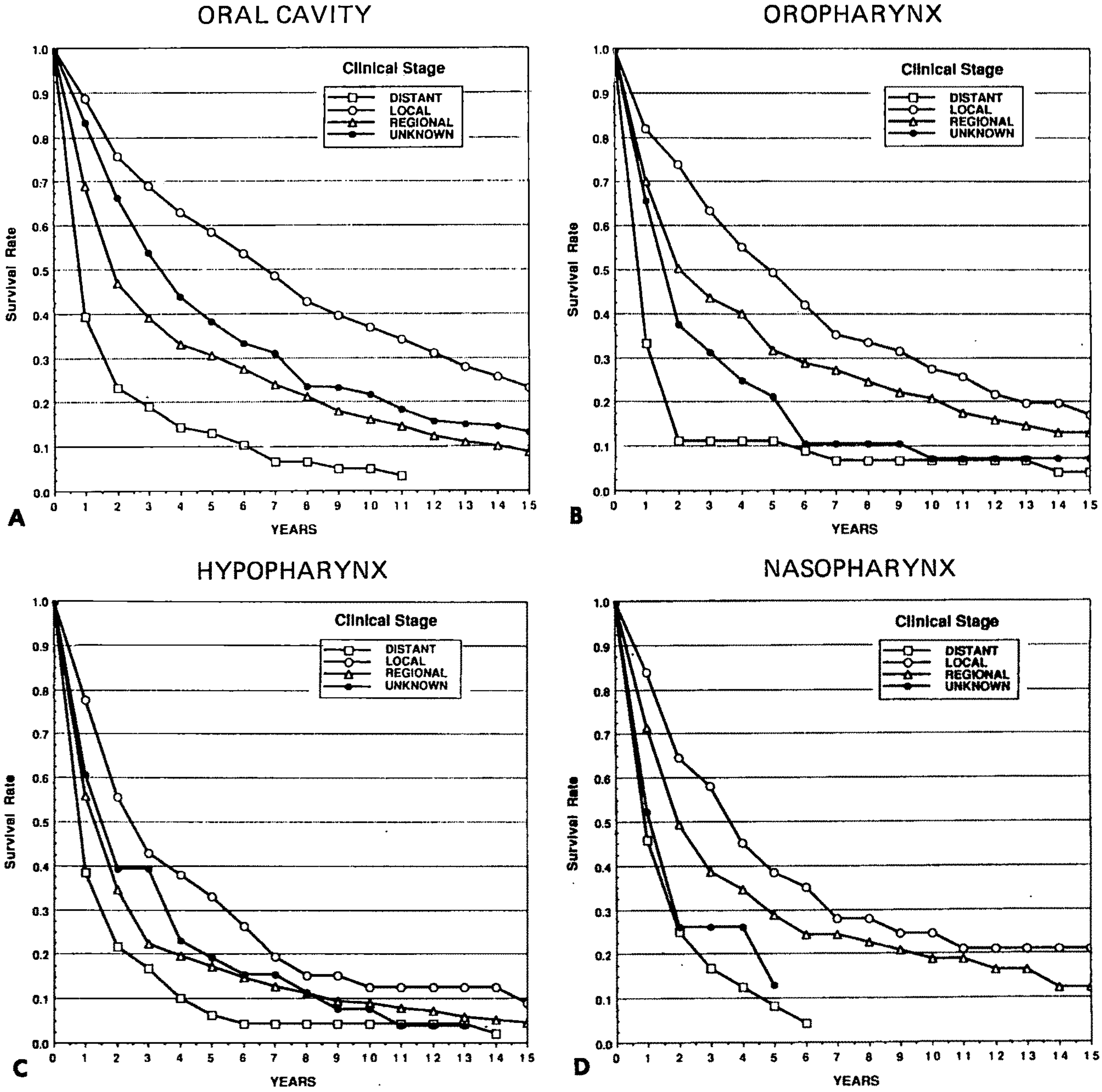

Fig 13. Actuarial survival curves by clinical stage for patients with cancers of A) oral cavity, B) oropharynx, C) hypopharynx, and D) nasopharynx, 1960 to 1985.

times during this period (Fig 9). Cobalt 60 teletherapy was available throughout the 26 years, having been first installed at UIHC in 1956. However, the first cobalt machine had limited capabilities because of a short (50 cm) source-skin distance (SSD), small source activity, and no capabilities for rotational therapy. Cobalt 60 teletherapy had only limited use during the first 3 years of the study.

The first rotational cobalt 60 teletherapy unit with a long SSD (80 cm) was installed in 1966 (Fig 9). This had a larger source and a longer SSD (80 cm). At the same time, the radiotherapy division moved into new facilities. A betatron with electron beam capabilities was acquired, and the first simulator was installed.

A 4-megavolt linear accelerator became available in 1976, and an 18-megavolt linear accelerator that was capable of producing 10-megavolt x-rays and 6- to 18-MeV electrons was installed in 1979. A variety of brachyradiotherapy sources were available throughout the period of the study, including radium tubes and needles, cesium tubes and needles (after 1981), gold 198 seeds (after 1972), and afterloading iridium 192 ribbons (after 1982).

Analysis showed that the expansion of the radiation oncology division and installation of supervoltage x-ray equipment, electron beam therapy, and

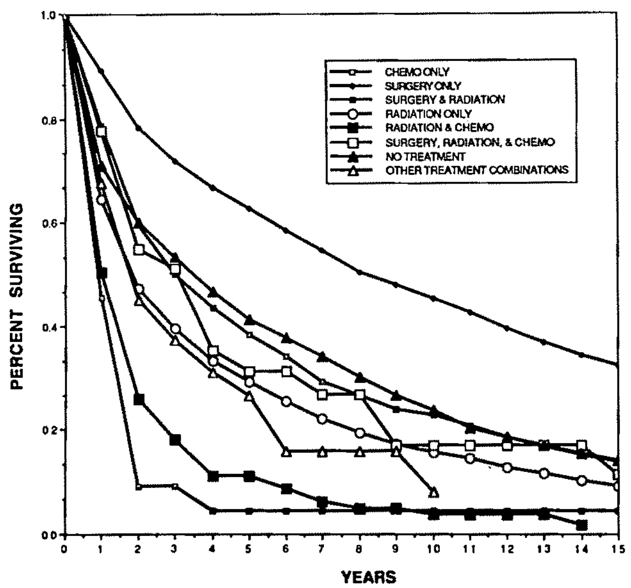

Fig 14. Actuarial survival by treatment method for 4,506 patients with head and neck cancer, 1960 to 1985.

afterloading brachyradiotherapy techniques had no detectable influence on the selection of treatment modality (ie, surgery versus radiotherapy versus combined therapy) for head and neck cancer patients at UIHC (Fig 9).

## SURVIVAL ANALYSIS

### TOTAL POPULATION

Actuarial survival (life table method) for the total population including all sites and stages is illustrated in Fig 10. Of the total group of 4,506 patients, 43.4% survived 5 years. This is a crude survival rate with no adjustments for age, death due to intercurrent disease, etc. The majority of the deaths occurred within the first 2 years. The actuarial survival rates at 2, 5, 10, and 15 years were 61.3%, 43.4%, 27.8%, and 18.4%, respectively. These are similar to the survival rates for head and neck cancer patients reported in the literature. In most series, more than 90% of the failures with head and neck cancer become apparent within 2 years.

### ANALYSIS BY STAGE

Patient survival correlated well with the clinical stage of the disease (Fig 11). Whereas 61.8% of the patients with tumor clinically limited to the primary site (localized disease) survived 5 years, only 30.2% of those with regional metastasis and 11.1% of those with distant metastasis did. Again, the majority of deaths occurred within the first several years. The 2-year survival rates for patients with local, regional, and distant metastasis stages were 79.1%, 48.7%, and 20.6%, respectively. Unstaged patients fared better than those with known regional or distant metastasis. This suggests that many of the unstaged patients had localized disease.

### ANALYSIS BY SITE

The results are compared by tumor site in Table 6. As expected, the survival rates for patients with lip, larynx, and salivary gland tumors were superior to those achieved for patients with cancers of other head and neck sites. Furthermore, the survival rate for patients with oral cavity cancers was slightly greater than the survival rate for patients with cancers of the oropharynx or hypopharynx. The actuarial survival rates for patients with oral cavity, oropharyngeal, hypopharyngeal, and nasopharyngeal cancers are compared in Fig 12.

Patient survival correlated well with the stage of the disease for all major regions (Table 7). For most sites, the 5-year survival rate for patients with disease localized to the primary site was approximately twice that observed for those with regional metastasis and five times that for patients with distant metastasis. Nasopharyngeal cancer was an exception because the long-term survival of those with regional lymph node metastasis (5-year survival rate = 28.9%) was only slightly poorer than the long-term survival of patients with disease localized to the primary site (5-year survival = 38.5%) (Fig 13). These results suggest that the presence of regional lymph node metastasis from nasopharyngeal cancer is less important with regard to prognosis than it is for other head and neck sites.

Survival rates for oral cavity, oropharyngeal, hypopharyngeal, and nasopharyngeal neoplasms are analyzed by stage of disease in Fig 13. In the oral cavity, 58.5% of patients with localized disease survived 5 years, compared to 30.6% of those with regional disease and 13% of those with distant metastasis (Fig 13A). In the oropharynx, 49% of those with localized disease survived 5 years, compared to 31.7% of those with regional disease and 11.1% of those with distant metastasis (Fig 13B). The survival rate for patients with cancer of the hypopharynx was poor, regardless of stage, but there was still a

TABLE 8. TWO- AND 5-YEAR SURVIVAL RATES AS FUNCTION OF CLINICAL STAGE AND TREATMENT MODALITY (ALL SITES)

| *Clinical* | *Surgery Alone* | | | *Radiotherapy Alone* | | | *Surgery and Radiotherapy* | | |
|---|---|---|---|---|---|---|---|---|---|
| *Stage* | *No.* | *2-y* | *5-y* | *No.* | *2-y* | *5-y* | *No.* | *2-y* | *5-y* |
| Localized (T1-4N0M0) | 973 | 85.9% | 72.3% | 494 | 68.8% | 46.2% | 189 | 81.5% | 59.9% |
| Regional metastasis (T1-4N1-3M0) | 392 | 60.9% | 41.7% | 573 | 36.1% | 19.0% | 666 | 56.4% | 35.9% |
| Distant metastasis (T1-4N0-3M1) | 35 | 37.1% | 25.7% | 137 | 14.1% | 7.9% | 72 | 30.6% | 15.7% |

Only most commonly used treatment modalities are shown.

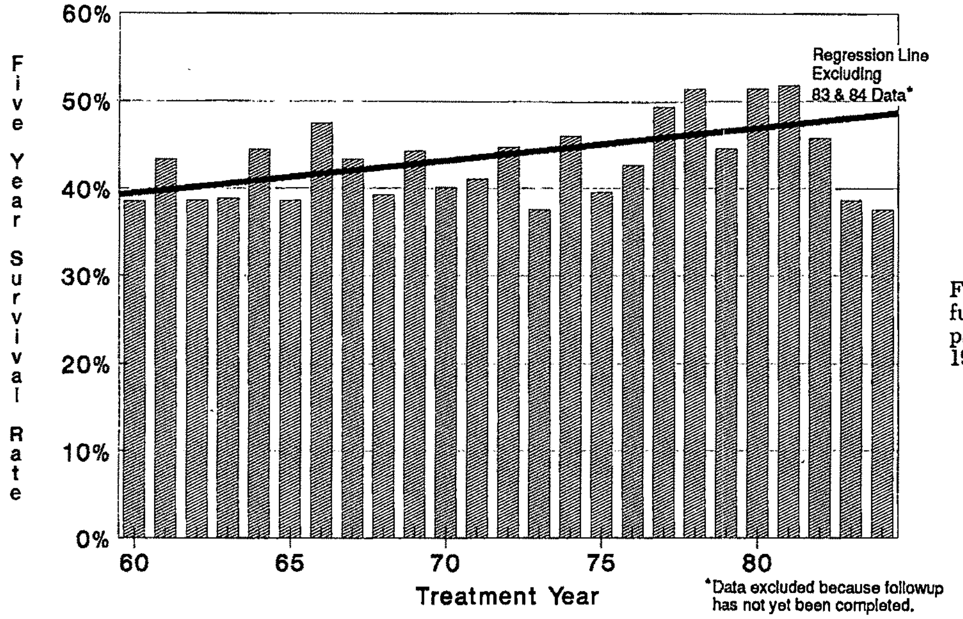

Fig 15. Five-year survival rate as function of treatment year for 4,506 patients with head and neck cancer, 1960 to 1985.

correlation with stage — 33% for patients with localized disease, 17.2% for those with regional disease, and 6.4% for those with distant metastasis (Fig 13C).

ANALYSIS BY TREATMENT MODALITY

Survival rates for the total population are compared by treatment modality in Fig 14. These data include all sites and stages. As expected, the 5-year survival rate of the group treated with surgery alone was superior to the survival rate of the groups treated with the other modalities, because patients treated with radiotherapy or combined surgery and radiotherapy had significantly more advanced cancers than those treated with surgery alone.

Similar findings were found when the data were analyzed by stage (Table 8). However, as previously described, there was a significant staging bias between the various treatment groups. In general, the most favorable cases were treated with surgery alone, whereas those with unfavorable characteristics were treated with radiotherapy alone or com-

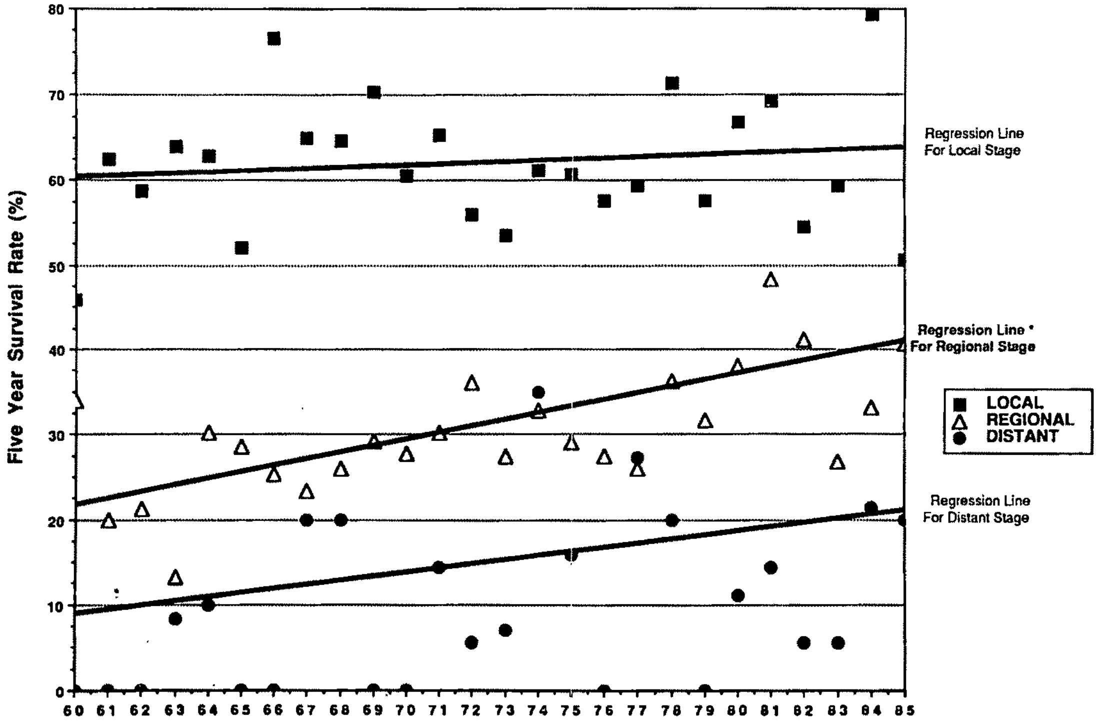

Fig 16. Five-year survival rates as function of treatment year by stage of disease for all staged patients with head and neck cancer, 1960 to 1985.

TABLE 9. TWO- AND 5-YEAR SURVIVAL RATES AS FUNCTION OF TREATMENT YEAR FOR ALL PATIENTS IN STUDY

| *Treatment Year* | *2-Year Survival* | *5-Year Survival* |
|---|---|---|
| 1960 | 53.8% | 38.6% |
| 1961 | 65.8% | 43.4% |
| 1962 | 52.9% | 38.7% |
| 1963 | 53.4% | 38.8% |
| 1964 | 62.4% | 44.5% |
| 1965 | 65.5% | 38.7% |
| 1966 | 62.2% | 47.5% |
| 1967 | 68.6% | 43.4% |
| 1968 | 55.2% | 39.3% |
| 1969 | 57.8% | 44.3% |
| 1970 | 57.4% | 40.1% |
| 1971 | 54.0% | 41.1% |
| 1972 | 63.8% | 44.8% |
| 1973 | 58.4% | 37.6% |
| 1974 | 58.4% | 46.0% |
| 1975 | 58.0% | 39.6% |
| 1976 | 62.4% | 42.7% |
| 1977 | 59.6% | 49.3% |
| 1978 | 69.2% | 51.3% |
| 1979 | 61.5% | 44.6% |
| 1980 | 73.7% | 51.4% |
| 1981 | 69.3% | 51.8% |
| 1982 | 62.1% | 45.8% |
| 1983 | 55.5% | 38.7% |
| 1984 | 61.4% | 37.6% |

bined modality treatment.

## ANALYSIS BY TREATMENT YEAR

Survival was analyzed by treatment year to determine whether the results had improved over the past three decades. This improvement was expected because there were significant advances in diagnostic and treatment techniques for head and neck cancers during this period. Computed tomography was developed in the early 1970s, and magnetic resonance imaging became available in the early 1980s. Advanced surgical techniques became available during this time with developments such as electrocoagulation, cryosurgery, and laser surgery. New reconstructive methods using pedicle grafts and free flaps made it possible to repair large surgical defects even in heavily irradiated tissues. In addition, improved maxillofacial prosthodontic techniques were developed to help restore function and cosmesis.

Radiotherapy techniques were also improved during this period with the development of supervoltage x-ray beams, electron beam therapy, and afterloading brachyradiotherapy techniques. Most important, radiation oncologists and surgeons developed a better understanding of dose-response relationships and the relative roles of surgery and radiotherapy in combined modality therapy. Moderate doses of radiation were shown to be very effective in the management of subclinical disease, while bulky tumors were found to be better treated with combined surgery and radiotherapy.

Five-year survival rates for the total population are plotted by treatment year in Fig 15. In this analysis, there was an improvement in survival over the 26-year period — from a 39% 5-year survival in 1960 to a 47% 5-year survival in 1984. This change is statistically significant (p = .05). This improvement in survival occurred even though there was a shift in stage distribution toward more advanced cases in the later years (Table 2).

When the data were analyzed by stage, the improvement in survival was found to be mainly due to better results for patients with regional disease (Fig 16). Regression analysis showed a slight improvement in survival for patients with localized cancers (from 60% in 1960 to 64% in 1985) and for patients with distant metastasis (from 9% in 1960 to 21% in 1985), but the differences were not statistically significant. The 5-year survival rate for patients with regional disease, however, improved from approximately 22% in 1960 to approximately 41% in 1985, and this trend is statistically significant (p = .05). The improvement in results for patients with regional disease could be due to a variety of factors, but it is possibly related to better use of postoperative radiotherapy.

The data were analyzed to determine whether the treatment selection criteria affected the results. During certain periods there was a greater tendency to use surgery alone, and during others there was more tendency to use radiotherapy alone or combined surgery and irradiation. No significant relationship between survival and the treatment philosophy that predominated during a particular era could be detected (Table 9 and Figs 9 and 15).

## CONCLUSIONS

1. The total number of patients with head and neck cancers and the distribution by anatomic site remained relatively stable over the 26-year period. However, there was a general trend toward more advanced stages in later years.

2. The selection of a treatment modality was primarily related to the site and stage of the disease, but there was also a correlation with the appointments of various surgical oncologists. There was no correlation between the selection of a treatment modality and the availability of specialized radiotherapy techniques or chemotherapeutic agents.

3. Patient survival rates correlated well with site and stage of disease.

4. There was a gradual improvement in 5-year survival rates over the 26-year period, from approximately 39% in 1960 to approximately 47% in 1984. This was principally due to an improvement in 5-year survival for patients with regional stage disease, from 22% in 1960 to 41% in 1985.

5. Although treatment philosophy varied to some degree with the appointments of various surgical oncologists, 5-year survival rates showed no correlation with changes in oncology personnel.

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ACKNOWLEDGMENTS — The authors thank Roberta Parks for support from the Tumor Registry, Lisa Smith and Theodore Yank for statistical analysis, and Terry Kirk for manuscript preparation.

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SUPPLEMENT 153 — MAY 1991
Volume 100, Number 5, Part 2

# ANKYLOGLOSSIA WITH DEVIATION OF THE EPIGLOTTIS AND LARYNX

SUSUMU MUKAI, MD
CHIKAKO MUKAI, MD
KAZUYUKI ASAOKA, MD

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SUSUMU MUKAI, MD
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KAZUYUKI ASAOKA, MD

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*Ann Otol Rhinol Laryngol* 100:1991

# ANKYLOGLOSSIA WITH DEVIATION OF THE EPIGLOTTIS AND LARYNX

SUSUMU MUKAI, MD

CHIKAKO MUKAI, MD

KAZUYUKI ASAOKA, MD

KANAGAWA, JAPAN

We observed ankyloglossia to be usually accompanied by displacement of the epiglottis and larynx. Infants with this disease developed dyspnea and skin and hair abnormalities. In addition, they had other symptoms, such as a dark forehead, a frowning expression, a dark color around the lips, scanty eyebrows, swelling around the palpebrae, harsh respiratory sounds, hard crying, snoring, and frequent yawning. In spite of these abnormalities, they had been considered to be healthy by their pediatricians. Arterial oxygen percent saturation (SaO2) was measured while the infants were asleep, suckling, and awake. The results revealed that their SaO2 was unstable and slightly low. The symptoms and signs of this disease were very similar to those observed in victims of sudden infant death syndrome before their death. Correction of the ankyloglossia and deviation of the epiglottis and larynx resulted in great improvement of these signs as well as a stabilization and increase of SaO2.

KEY WORDS — ankyloglossia, dyspnea, epiglottis, frenulum, larynx, sudden infant death syndrome.

## INTRODUCTION

*Ishinhou*, the oldest extant Japanese medical book,[1] describes frenotomy being used when ankyloglossia or tongue-tie was observed in newborn babies. Frenotomy has been performed at least since the Chou era (1050-256 BC) in China.[2] In the Middle Ages in France, at baptism a midwife would inspect the frenulum linguae and cut it with her little fingernail when tongue-tie was present. If suckling difficulties persisted she would repeat the procedure on the third day.[3] Apparently, this practice was also common in other European countries.[4]

Nowadays in Europe and America, clinicians deny the relationship between ankyloglossia and suckling difficulties. Illingworth says, "There are still doctors who cut the frenulum in the new-born period. This is always wrong."[5] In Western countries ankyloglossia is discussed only in relation to articulation and malocclusion.[6] We found no systematic studies about the relationship between ankyloglossia and suckling, except for two cases reported in English by Cullum.[4]

In 1948, in Japan, Shiina[7] found 138 cases (59.2%) of ankyloglossia among 233 newborn babies; 98 of the 138 patients underwent frenotomy, and he observed improvement of suckling abilities in all of them. Shimizu and Matsuda[8] also reported an increase of suckling abilities after frenotomy of both the frenulum linguae and the frenulum labii superioris. From 1975 to 1988, they treated 3,940 patients, of whom 93.6% showed improvement. Matsuda et al[9] reported that ankyloglossia was an autosomal dominant congenital anomaly. Oketani[10] observed that babies with tongue-tie and/or short tongues not only had suckling difficulties but also had other symptoms, such as inactivity and either too slow or too fast development. The need for frenotomy in babies with ankyloglossia has been emphasized in Japan, especially among midwives[11] (also unpublished observations, Suzuki and Katagili,

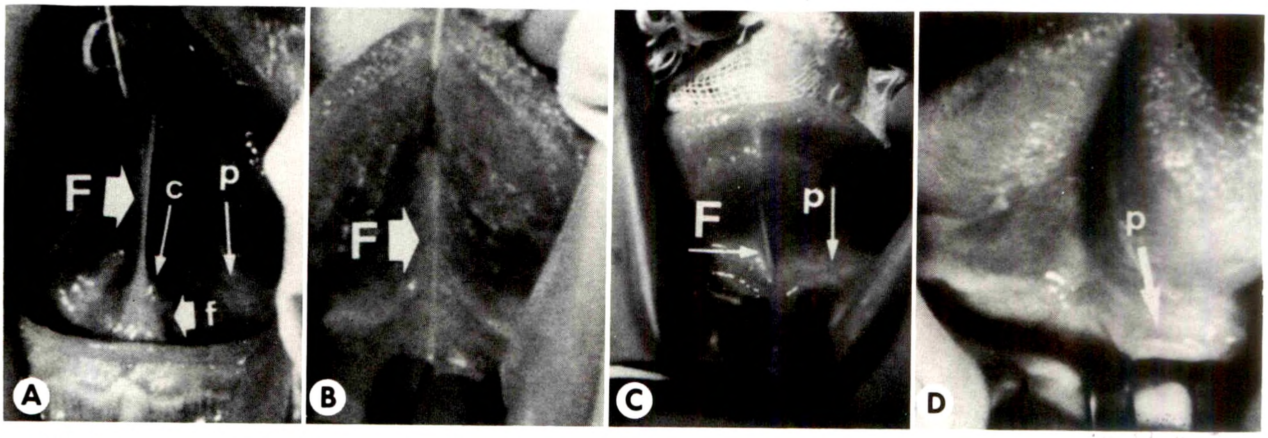

Fig 1. Categories of frenulum linguae (F) and base of tongue (see text, p 5). A) F3B1. B) F2B2. C) F1B3. D) F0B3. f — frenulum starting from mandibular alveolar border, p — plica sublingualis, c — caruncula sublingualis.

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From the Mukai Clinic and Research Institute of Biology, Kanagawa, Japan.

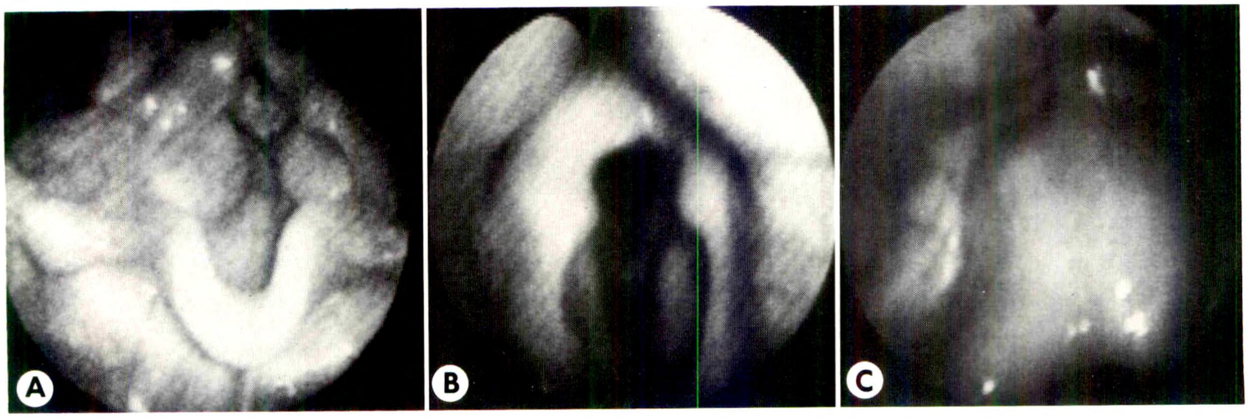

Fig 2. Fiberscopic view from nasopharynx of epiglottis and larynx. A) Type A. Epiglottis stands toward nasopharynx, larynx is in its normal position, and full abduction of vocal folds is observed during inspiration. B) Type B. Epiglottis leans toward radix linguae. Larynx is up and elongated by hypopharyngeal walls. Vocal cords do not abduct fully in inspiratory phase. C) Type B. Larynx is elongated upward and curved toward radix linguae.

1989, and Yoshimi and Ajimoto, 1989). We have noticed that newborn babies and suckling infants with ankyloglossia present mild dyspnea as well as typical skin and hair signs. Moreover, these patients have deviation of the epiglottis and of the larynx.[12-14] We thought that all these signs might characterize a single congenital abnormality, and therefore we investigated the relationship between the degree of ankyloglossia and the deviation rate of the epiglottis and larynx, the arterial oxygen saturation rate, skin and hair signs, and other symptoms that we have noticed in newborn and suckling infants.

Here, we report the results of the surgical procedure we have established to correct this anomaly. We also discuss the relationship between this anomaly and sudden infant death syndrome (SIDS), for the observed symptoms are quite similar to those reportedly found in SIDS.[15-17]

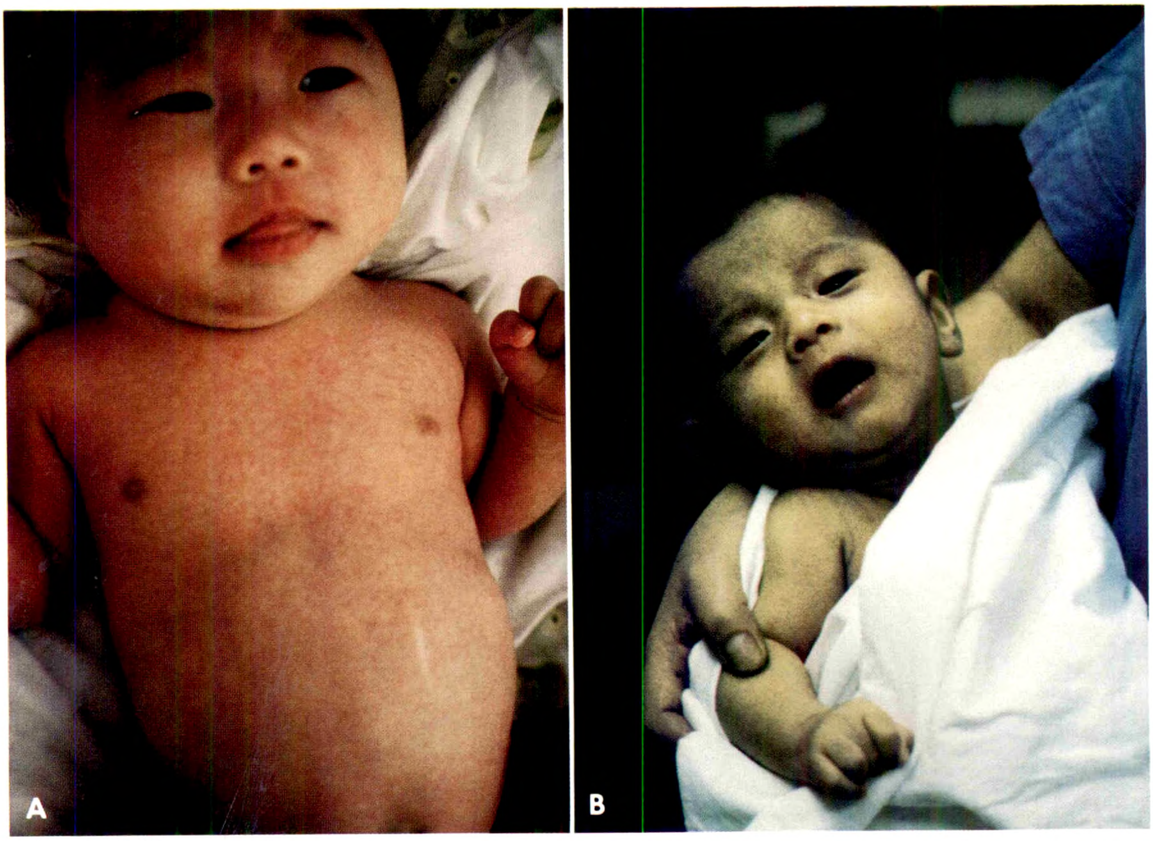

Fig 3. Characteristics of skin. A) Marbled. Also notice dark forehead, frowning expression, swelling around palpebrae, forward location of tongue, hollowed fronto-orbital region and hypertrophy in lower part of cheek, slight retraction of chest, and pigmentation of skin by nail wall. B) Cyanotic. Also notice thin fingers, scanty hair, dark lips, and exhausted face.

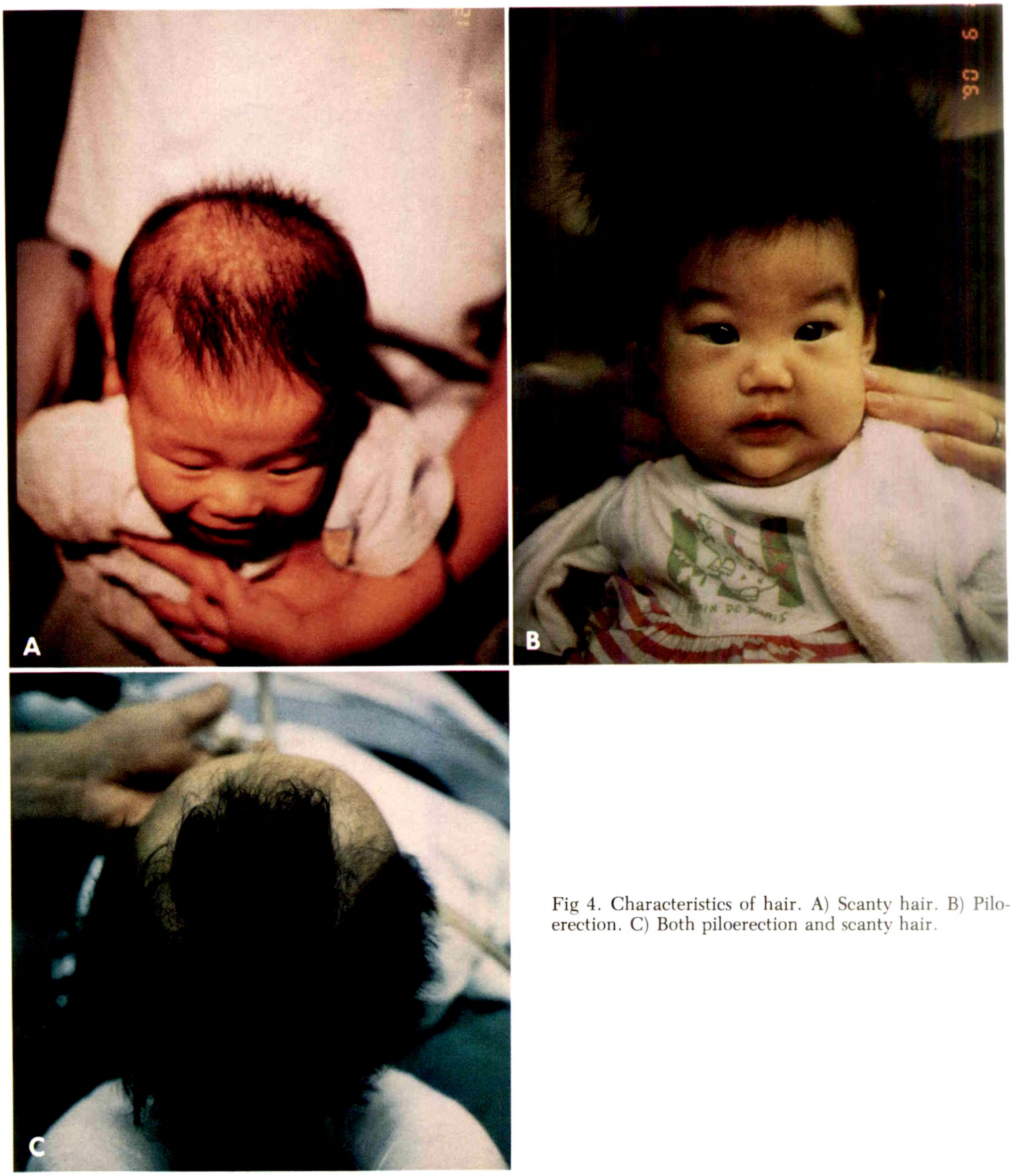

Fig 4. Characteristics of hair. A) Scanty hair. B) Piloerection. C) Both piloerection and scanty hair.

## PATIENTS AND OBSERVATIONS

Fifty-one patients with ankyloglossia who visited the otorhinolaryngology division of Mukai Clinic from May to December 1989 were entered in this study. The patients' ages ranged from 3 to 59 weeks. After the clinical examination was completed, 46 patients were operated on to correct the ankyloglossia and dislocation of the epiglottis and larynx. We classified 1) ankyloglossia, 2) deviation of the epiglottis and the larynx, 3) arterial oxygen saturation rate, and 4) skin and hair signs as described below.

### ANKYLOGLOSSIA

Ankyloglossia (Fig 1) was observed in relation to abnormalities of the frenulum linguae and to variations in the origin of the free portion of the tongue.

*Frenulum Linguae*. On the basis of the degree of the tied state of the tongue, we classified the frenulum anomalies into four grades.

1. Grade F3 (Fig 1A). The frenulum went from the mandibular alveolar border to the tongue.
2. Grade F2 (Fig 1B). The frenulum went from the caruncula sublingualis to half the distance between the floor of the mouth and the tip of the tongue.
3. Grade F1 (Fig 1C). The frenulum went from the caruncula sublingualis to the lower portion of the tongue.
4. Grade F0 (Fig 1D). No frenulum was observed.

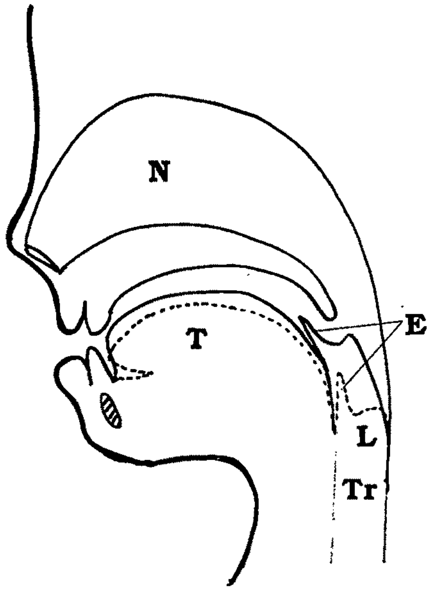

Fig 5. Conception of correction of deviation of tongue (T), epiglottis (E), and larynx (L). Solid line — preoperative, dotted line — postoperative, Tr — trachea, N — nose.

*Base of Free End of Tongue*. On the basis of the origin of the free end of the tongue, we classified the different types of patients into three groups.

1. Grade B3 (Fig 1C,D). Those patients in whom the base of the tongue was about 5 mm from the plica sublingualis and the plica sublingualis was barely mobile.
2. Grade B2 (Fig 1B). Those patients in whom the free end of the tongue originated at a point more than 5 mm from the plica and in whom it was pulled up during the examination.
3. Grade B1 (Fig 1A). Those patients in whom the caruncula and plica sublingualis were mobile and remained in position when the tip of the tongue was held up during the examination.

Ankyloglossia was diagnosed when the frenulum linguae was classified as F3 and/or the base of the tongue was classified as B2 or B3.

## EPIGLOTTIS AND LARYNX

Fiberscopy was carried out to examine the epiglottis and the larynx. Fiberscopes (30p II Machida, Yokohama, Japan) were employed via the nose.

*Epiglottis*. Normally the epiglottis stands upright, toward the nasopharynx. The position of the epiglottis was classified into one of two categories. In type A, the epiglottis was in the normal position (Fig 2A). In type B, the epiglottis leaned toward the radix linguae or was hard to see in its entirety from the nasopharynx (Fig 2B,C).

*Larynx*. The position of the larynx was classified into one of two categories. In type A, the larynx was situated in its normal position and the vocal folds were fully abducted during inspiration (Fig 2A). In type B, the larynx was elongated upward and curved toward the radix linguae. Also, 1) during phonation the vocal folds were hard to see, because the plicae aryepiglottica, tubercula corniculum, and tubercula cuneiform moved over them, and/or 2) full abduction of the vocal fold during inspiration was not observed (Fig 2B,C). The preoperative conditions and the postoperative changes were videotaped (Sony VO 9850 and Victor HA SC-1000, Tokyo, Japan).

*Arterial Oxygen Percent Saturation*. The arterial oxygen percent saturation (Sa$O_2$) was measured during sleep, during suckling, and while the infant was awake with a pulse oximeter (CSI 502, Tokyo, Japan) with disposable sensors made for infants (CSI 572 or 573). During the measurements the pulse waves were always confirmed. The duration of the measurements was as follows. During sleep, Sa$O_2$ was measured from the time the babies fell asleep until they woke up; during suckling, it was measured from the beginning to the end of suckling. In the awake state, it was measured for about 15 minutes. Patients were classified into two groups according to their Sa$O_2$: 1) type A, when Sa$O_2$ was within the normal range (99% to 96%), or 2) type B, when Sa$O_2$ was 95% or below.

*Skin and Hair*. In our observations, the patients had normal, marbled, or cyanotic skin; their hair was normal or scanty or showed piloerection (Figs 3 and 4). Although there were patients in whom two features were observed, they were classified according to the predominant sign.

*Other Symptoms*. We observed other symptoms that are described in Results.

## SURGICAL CORRECTION

In ankyloglossia with dislocation of the epiglottis and larynx, the tongue is located forward, and as a result the epiglottis has moved up and leans toward the mouth. The larynx is also raised and curves ventrally. The objective of operating is to move the epiglottis and the larynx downward, so that they stand in the normal relation to the nasopharynx, by cutting the connective tissue of the tongue, including the septum linguae and the front bundles of the genioglossal muscles (Fig 5). This operation includes frenotomy, if a frenulum linguae exists, and corrections of the deviation of the tongue, the epiglottis, and the larynx.[14]

## STATISTICAL ANALYSIS

Patients were divided into three groups according to their age. The $\chi^2$ test and Student's *t* test were used in the statistical analysis of the various parameters studied and the relationships among them.

## RESULTS

Clinical data corresponding to the study group presented here are summarized in Table 1. Except

TABLE 1. PATIENT DATA

| *Case* | *Sex* | *Age (wk)* | *Base of Tongue* | *Fnl* | *Egl* | *Larynx* | *Skin* | *Hair* | *Slp* | *Sck* | *Awk* | *Pslp* | *Psck* | *Pawk* | *Others* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 3 | 3 | 0 | B | B | C | B | B | A | B | A | A | A | NO, VCN, A85 |
| 2 | M | 3 | 2 | 1 | A | B | C | B | B | B | B | B | B | B | VCN |
| 3 | F | 4 | 1 | 3 | B | B | B | B | B | B | B | A | A | A | |
| 4 | F | 4 | 1 | 3 | B | A | B | C | B | B | B | A | A | A | A85 |
| 5 | M | 4 | 3 | 0 | B | B | B | B | B | B | A | A | B | A | JVC, A85 |
| 6 | M | 4 | 1 | 3 | B | B | A | A | B | B | A | A | A | A | |
| 7 | M | 5 | 2 | 0 | A | B | B | C | B | B | A | A | A | A | A85 |
| 8 | M | 5 | 2 | 3 | A | B | C | C | A | B | B | A | B | A | |
| 9 | F | 5 | 3 | 1 | B | B | B | B | B | B | A | A | A | A | Snore |
| 10 | F | 5 | 2 | 2 | A | B | B | B | B | B | B | B | B | A | NO, VCN |
| 11 | F | 5 | 2 | 2 | A | A | B | C | B | B | B | N | N | N | Not operated |
| 12 | F | 6 | 3 | 0 | B | B | B | C | B | B | B | A | B | B | VCN |
| 13 | F | 6 | 3 | 1 | B | B | B | B | B | B | B | A | A | A | A85 |
| 14 | M | 7 | 1 | 3 | B | B | B | C | B | A | A | A | A | A | A85 |
| 15 | M | 8 | 2 | 2 | A | B | B | A | B | B | B | A | A | A | |
| 16 | M | 8 | 3 | 1 | B | B | C | C | B | A | A | A | A | A | A85 |
| 17 | F | 8 | 2 | 2 | A | B | B | B | B | A | A | A | A | A | Slp apn |
| 18 | F | 8 | 1 | 3 | A | B | B | B | B | A | A | A | B | A | Snore, A85 |
| 19 | M | 8 | 3 | 2 | A | A | B | C | B | A | A | A | A | A | Slp apn |
| 20 | M | 9 | 2 | 3 | A | B | B | C | B | B | B | N | N | N | Not operated |
| 21 | M | 9 | 2 | 2 | B | A | B | C | B | A | B | A | A | A | A85 |
| 22 | M | 9 | 3 | 1 | B | B | B | B | A | B | A | N | N | N | JVC, not operated |
| 23 | F | 10 | 2 | 2 | A | A | B | C | B | B | A | A | B | A | A85 |
| 24 | F | 10 | 3 | 3 | B | B | C | C | B | B | B | A | B | A | A85 |
| 25 | M | 11 | 1 | 3 | B | B | B | B | B | A | A | A | A | A | |
| 26 | F | 11 | 3 | 0 | A | B | C | A | B | A | B | A | A | A | A85 |
| 27 | M | 11 | 2 | 2 | B | B | B | B | B | A | A | A | A | A | A85 |
| 28 | F | 11 | 2 | 1 | A | B | B | C | B | A | A | A | A | A | A85 |
| 29 | F | 12 | 2 | 3 | B | B | B | B | B | B | B | A | B | A | Slp apn |
| 30 | F | 14 | 3 | 0 | A | B | B | B | B | B | A | A | A | A | Snore, A85 |
| 31 | F | 15 | 3 | 1 | B | B | B | C | B | A | B | A | A | A | NO, Snore |
| 32 | M | 15 | 3 | 1 | B | B | C | B | B | A | A | A | A | A | A85, near miss |
| 33 | M | 15 | 2 | 2 | A | B | A | C | A | A | A | A | A | A | NO |
| 34 | M | 15 | 3 | 1 | B | B | A | B | B | B | B | A | A | A | |
| 35 | F | 17 | 3 | 0 | A | B | C | C | B | B | B | A | A | A | |
| 36 | F | 18 | 2 | 3 | A | B | B | C | B | B | B | N | N | N | Slp apn, not operated |
| 37 | F | 18 | 3 | 3 | B | B | B | C | B | B | B | A | B | A | Slp apn |
| 38 | F | 19 | 3 | 0 | B | B | B | C | B | B | B | A | A | A | |
| 39 | M | 19 | 2 | 3 | B | B | B | C | A | B | A | A | A | A | |
| 40 | M | 20 | 2 | 2 | A | B | B | C | B | A | A | N | N | N | Not operated |
| 41 | M | 22 | 2 | 3 | A | B | C | B | A | A | A | A | A | A | |
| 42 | F | 26 | 3 | 2 | A | B | B | A | B | B | B | A | B | A | Premature, A85 |
| 43 | F | 37 | 3 | 0 | A | A | C | C | B | A | B | N | N | N | Not operated |
| 44 | F | 37 | 3 | 0 | B | A | B | C | A | A | A | A | A | A | |
| 45 | F | 39 | 1 | 3 | B | B | B | B | A | B | A | A | A | A | |
| 46 | F | 43 | 3 | 0 | A | B | A | A | A | A | A | A | A | A | |
| 47 | F | 43 | 3 | 0 | B | B | A | A | A | A | A | A | A | A | |
| 48 | F | 46 | 2 | 3 | B | B | A | C | A | A | A | A | A | A | |
| 49 | M | 54 | 2 | 2 | B | B | A | A | B | A | A | A | A | A | Muscle atony |
| 50 | M | 59 | 2 | 2 | B | B | A | A | A | A | A | A | A | A | |
| 51 | F | 59 | 1 | 3 | A | A | A | B | A | A | A | A | A | A | Snore |

See text for definition of categories.

Fnl — frenulum, Egl — epiglottis, Slp — SaO2 during sleep, Sck — SaO2 during suckling, Awk — SaO2 awake, P — SaO2 postoperation, Others — other chief complaints and symptoms, NO — nasal obstruction, VCN — vocal cord nodule, JVC — jaundice on vocal cord, Slp apn — sleep apnea, A85 — SaO2 during sleep decreased below 85%, near miss — near-miss episode of sudden infant death syndrome.

for one patient (No. 42), all patients were born after full-term pregnancy periods. Forty-four (86.3%) of them visited our clinic because of suckling difficulties after consulting with personnel at health centers or with midwives. Five patients (Nos. 1, 10, 31, 33, and 51) were brought to us because their parents thought they had nasal obstruction. Two (Nos. 2 and 12) were brought to us at the suggestion of friends because they cried too hard. Five patients (Nos. 17, 19, 29, 36, and 37) had apneic episodes during sleep besides suckling difficulties, and two (Nos. 5 and 28) had already undergone frenotomy at other clinics. Patient 49 was diagnosed as having central muscle atony and patient 32 had a history of

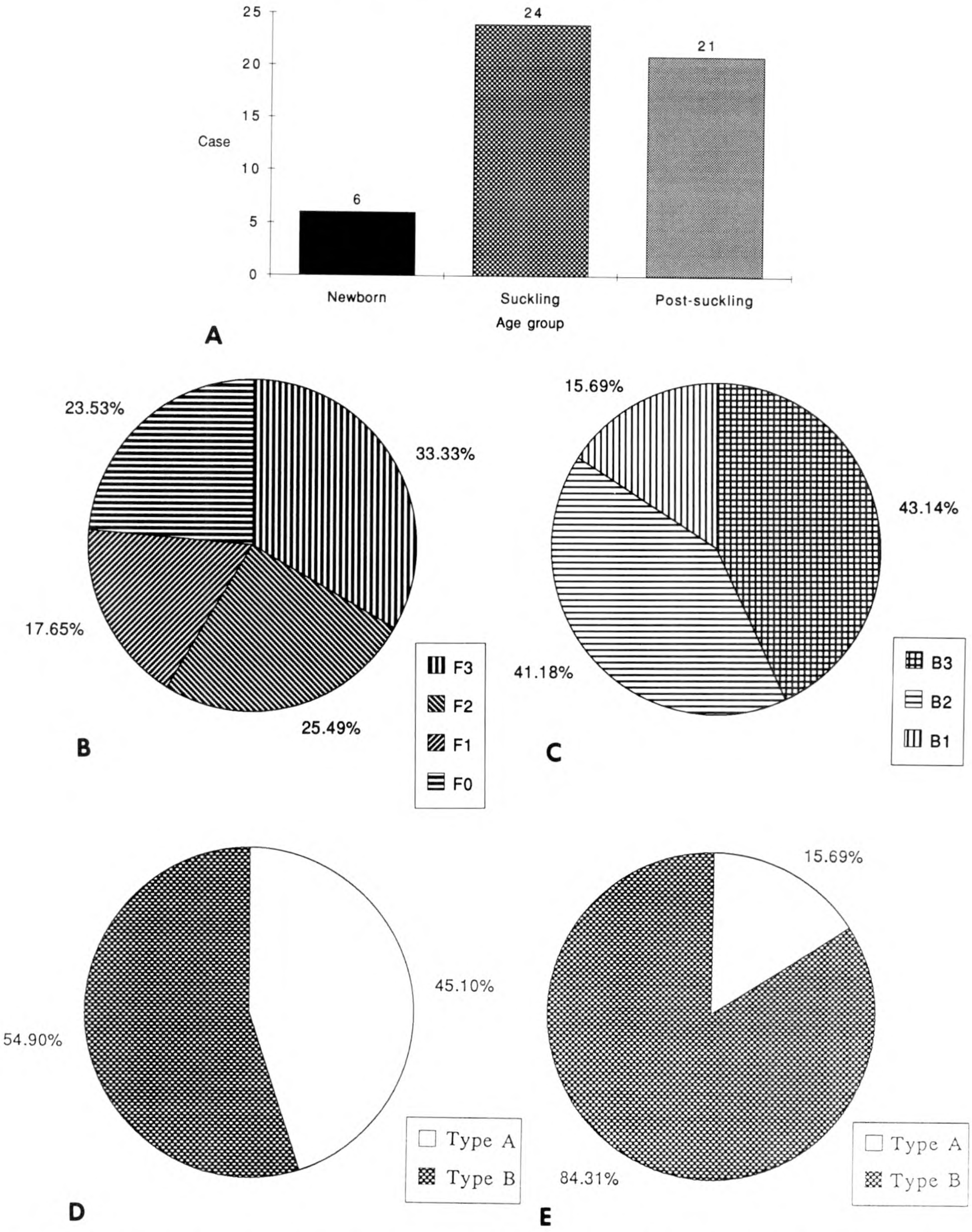

Fig 6. Distributions. A) Age groups. B) Types of frenulum (see text). C) Types of base of tongue (see text). D) Types of epiglottis. Type A — normal position, type B — leaning toward radix linguae or hard to see in entirety from nasopharynx. E) Types of larynx. Type A — normal position, with vocal folds fully abducting during inspiration, type B — elongated upward and curved toward radix linguae.

a near-fatal episode resembling SIDS. Patients were classified into three stages according to their ages: newborn (3 to 4 weeks), suckling (5 to 14 weeks), and post-suckling (15 to 60 weeks). The distribution of patients according to age group is shown in Fig 6A.

ANKYLOGLOSSIA

Clinical examination of the patients gave the following results for the frenulum: F3, 17 cases (33%); F2, 13 cases (25%); F1, 9 cases (18%); and F0, 12 cases (24%) (Fig 6B). The distribution of the frenulum types by age group is shown in Table 2. For the base of the tongue, results were as follows: B3, 22 cases (43%); B2, 21 cases (41%); and B1, 8 cases (16%) (Fig 6C). The distribution of types of base of tongue by age group is shown in Table 2. There was no significant difference among the newborn, suck-

TABLE 2. TYPES OF BASE OF TONGUE AND FRENULUM BY AGE GROUP

| | *Newborn* | *Suckling* | *Post-suckling* | *Total* |
|---|---|---|---|---|
| Base of tongue* | | | | |
| B1 | 3 | 3 | 2 | 8 |
| B2 | 1 | 12 | 8 | 21 |
| B3 | 2 | 9 | 11 | 22 |
| Total cases | 6 | 24 | 21 | 51 |
| Frenulum† | | | | |
| F0 | 2 | 4 | 6 | 12 |
| F1 | 1 | 5 | 3 | 9 |
| F2 | 0 | 8 | 5 | 13 |
| F3 | 3 | 7 | 7 | 17 |
| Total cases | 6 | 24 | 21 | 51 |

See text for definition of categories.

*$\chi^2 = 6.9405$ (not significant).

†$\chi^2 = 5.3445$ (not significant).

TABLE 3. RELATIONSHIP BETWEEN TYPES OF BASE OF TONGUE OR FRENULUM AND TYPES OF EPIGLOTTIS

| | *Epiglottis* | |
|---|---|---|
| | *A* | *B* |
| Base of tongue* | | |
| B3 | 7 | 15 |
| B2 | 14 | 7 |
| B1 | 2 | 6 |
| Total | 23 | 28 |
| Frenulum† | | |
| F3 | 6 | 11 |
| F2 | 9 | 4 |
| F1 | 2 | 7 |
| F0 | 6 | 6 |
| Total | 23 | 28 |

See text for definition of categories.

*$\chi^2 = 6.8178$; $p < .02$.

†$\chi^2 = 4.115$ (not significant).

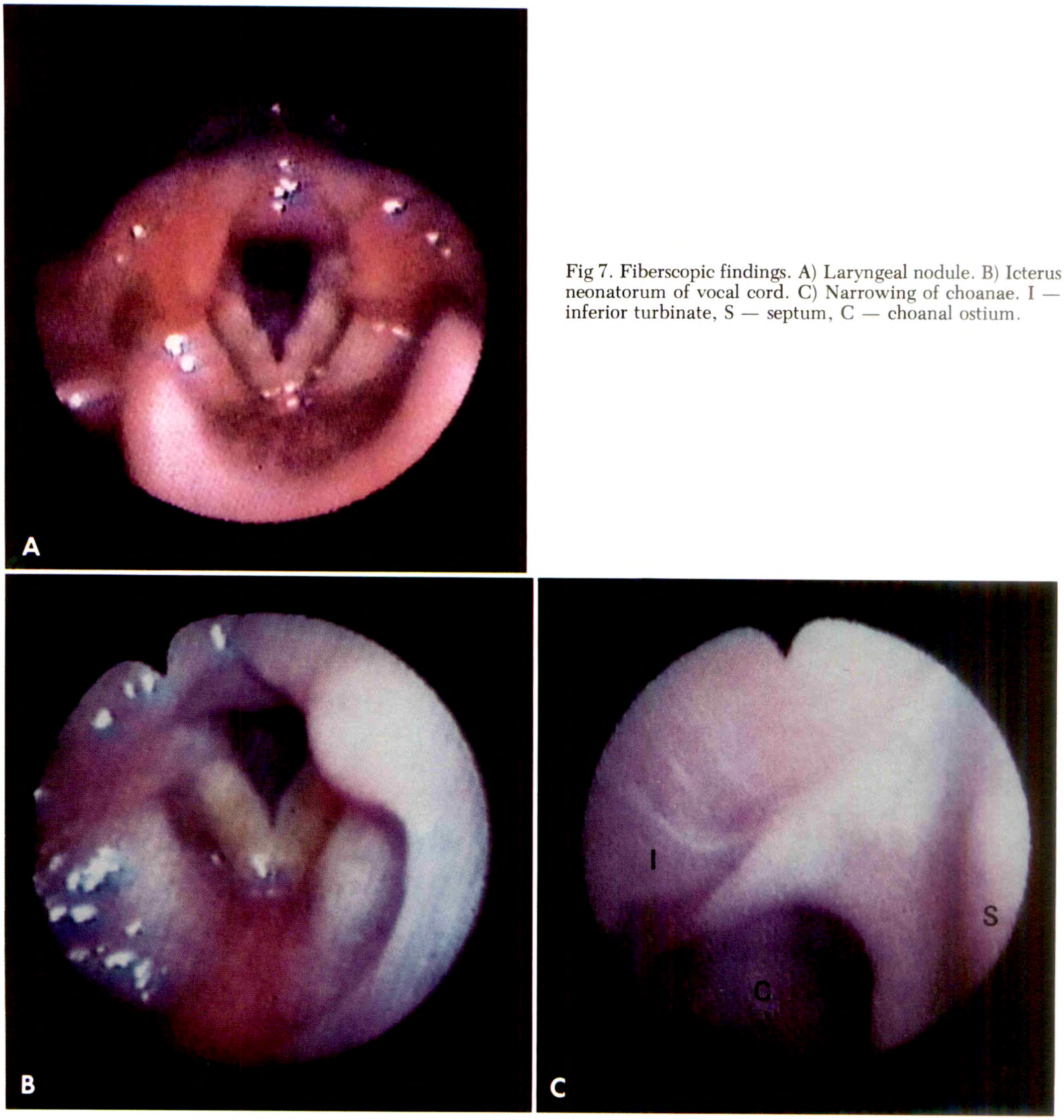

Fig 7. Fiberscopic findings. A) Laryngeal nodule. B) Icterus neonatorum of vocal cord. C) Narrowing of choanae. I — inferior turbinate, S — septum, C — choanal ostium.

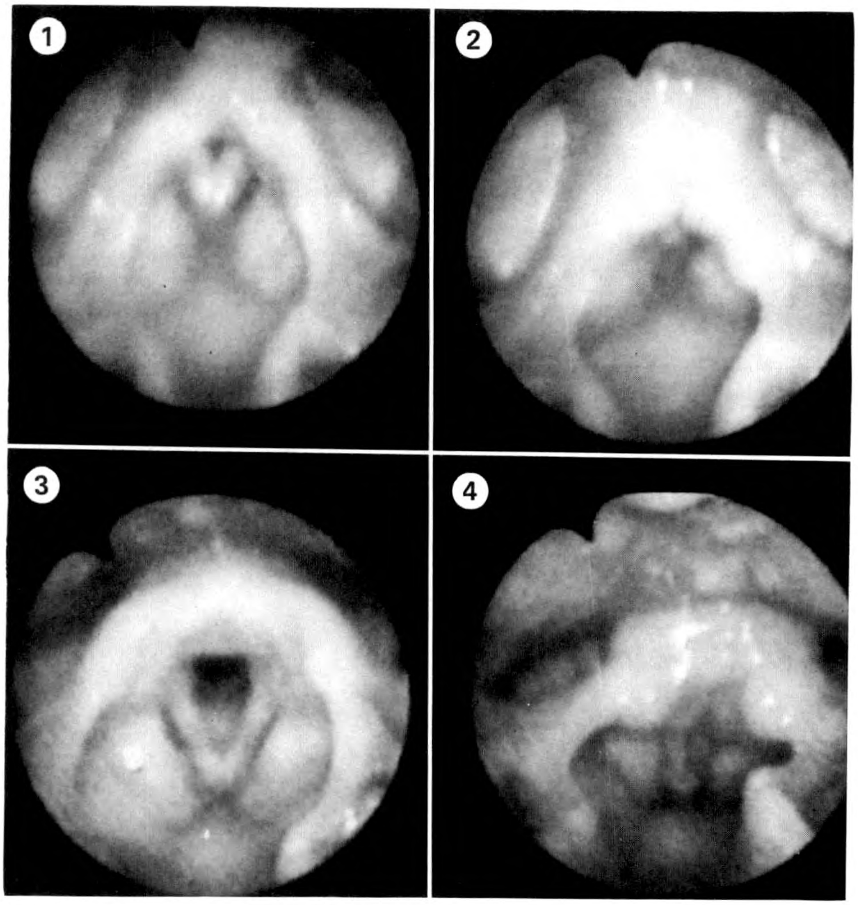

Fig 8. Epiglottis and larynx. After operation, epiglottis and larynx are lower in position, vocal cords adduct fully, and epiglottis stands toward nasopharynx. Preoperative (1 and 2) and postoperative (3 and 4) views during inspiration (1 and 3) and phonation (2 and 4).

ling, and post-suckling groups of patients regarding the distribution of the frenulum and base of the tongue characteristics. In this study population there were 37 cases that fell in the category B3 or F3 or both; 11 cases were both B2 and F2; and two patients had already undergone frenotomy.

EPIGLOTTIS AND LARYNX

According to the position of the epiglottis before the operation, there were 23 cases (45%) of type A and 28 cases (55%) of type B (Fig 6D). Regarding the position of the larynx, there were 8 cases (16%) of type A and 43 cases (84%) of type B (Fig 6E). When the epiglottis leaned to the left or to the right, the babies were able to suck only one of their mother's breasts. We did not observe nasal obstruction in the babies whose chief difficulty was said to be nasal obstruction, but their vocal cords were less abducted than normal (Fig 2B). Moreover, in three patients, vocal fold nodules were observed (Fig 7A). In two patients the membrane of their vocal folds presented remains of icterus neonatorum, but their skin did not (Fig 7B). None of the patients had adenoidal hypertrophy, tonsillar hypertrophy, or laryngomalacia, but narrowing of the choanae was observed in 12 cases (24%) (Fig 7C). There was no significant difference among newborn, suckling, and post-suckling groups of patients regarding the position of the epiglottis and the larynx. A direct relationship was observed between the status of the base of the tongue and the position of the epiglottis ($p < .02$), but not between the positions of the frenulum and the epiglottis (Table 3).

In all 26 (100%) patients who had a displaced epiglottis before the operation, the epiglottis stood in its normal upright position after the operation. In all patients who were operated on, the position of the larynx improved significantly in 35 cases (78%), improved slightly in 4 cases (9%), and remained in its normal position in 6 (13%) (Fig 8). Full abduction of the vocal folds was observed in all the patients who were operated on.

ARTERIAL OXYGEN PERCENT SATURATION

Results of the $SaO_2$ measurements at the patients' first clinical examination during sleep, during suckling, and while awake were as shown in Fig 9. In 76% of the cases there was a decrease of $SaO_2$ during sleep. During suckling the percentage was 53% and while awake it was 45%. The intergroup distribution of $SaO_2$ was as shown in Table 4.

*During Sleep*. The $SaO_2$ ratio of type A to type B in each group is shown in Fig 10. Statistical analysis revealed that $SaO_2$ during sleep varied significantly according to the patients' age ($p < .005$). We observed two types of $SaO_2$ decrease: one was an unstable $SaO_2$ that fell below 95% at times (Fig 11A),

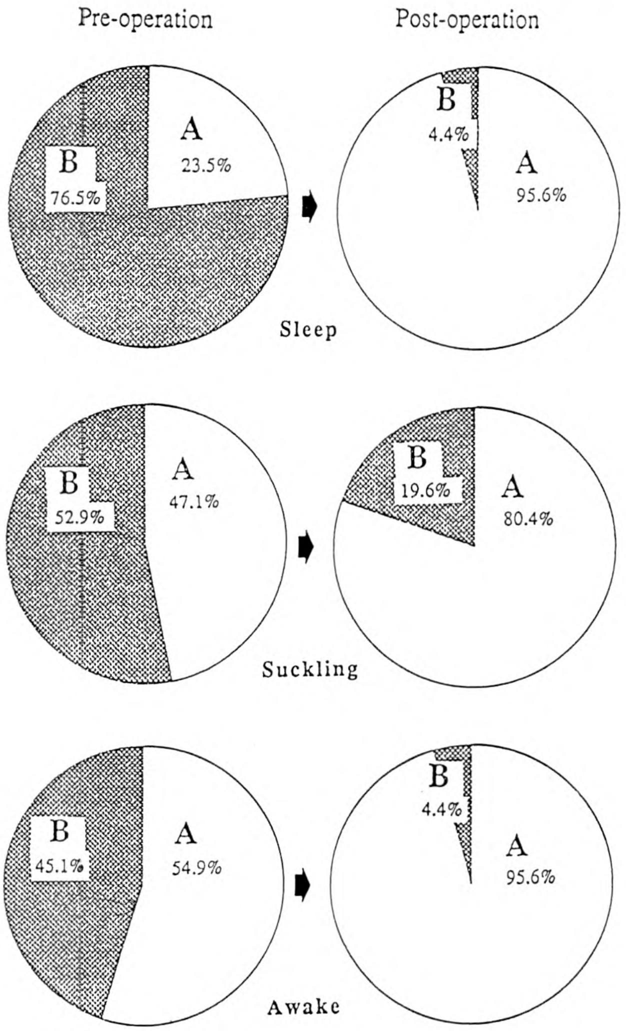

Fig 9. Preoperative and postoperative arterial oxygen percent saturation (SaO2) during sleep, during suckling, and while awake. Type A — within normal range (99% to 96%), type B — 95% or below.

and the other was an SaO2 that was constant for a while after the babies fell asleep but then suddenly fell below 95% (and the babies awoke) (Fig 12A). A decrease in SaO2 below 95% was always accompanied by a decrease in pulse rate (Fig 13).

There were 17 patients in whom the SaO2 fell below 85% (Table 1). All these patients were younger than 16 weeks of age, except for patient 42 (born prematurely), who was 26 weeks old. The mothers of some of the patients said that their babies stopped breathing at times; according to our observations, these halts of breath lasted 1 to 2 seconds. Some of the patients could not fall asleep; others did not fall asleep unless they were sucking their mothers' nipples. They woke up very easily. In those patients whose SaO2 did not fall below 95%, it oscillated between 99% and 97% during sleep.

*During Suckling*. The A:B ratio of the SaO2 of each group during suckling is shown in Fig 14. Although there was no significant difference with regard to SaO2 among the three groups of patients, we noted three types of suckling difficulties. In the first, the patient started sucking and his or her pulse rate increased, but then it suddenly decreased, and at the same time the SaO2 fell below 95%; simultaneously, the patient choked with coughing and could not continue sucking. Sometimes the patient cried loudly and after breathing several times he or she could recommence sucking (Figs 11B and 15A). In the second type of difficulty, the patient's pulse rate increased to 170 or more, and while it was high he or she stopped sucking (Fig 16), sometimes to start again when the pulse rate went back to normal, or to finish suckling with an increased pulse rate (Fig 17). During the sucklings, the SaO2 was at the maximum value of 99%. The babies fell asleep during and/or just after finishing sucking when they presented either of the two suckling problems described above. The third type of problem was one in which the patients continued sucking but it was difficult for their mothers to tell whether they had stopped sucking or not.

TABLE 4. INTERGROUP DISTRIBUTION OF ARTERIAL OXYGEN PERCENT SATURATION DURING SLEEP, SUCKLING, AND WHILE AWAKE

| | | *Asleep* | | *Suckling* | | *Awake* | |
|---|---|---|---|---|---|---|---|
| *Age Group* | *Cases* | *A* | *B* | *A* | *B* | *A* | *B* |
| Newborn (3 to 4 wk) | 6 | 0 | 6 | 1 | 5 | 2 | 4 |
| Suckling (5 to 14 wk) | 24 | 2 | 22 | 10 | 14 | 13 | 11 |
| Post-suckling (19 to 59 wk) | 21 | 10 | 11 | 13 | 8 | 13 | 8 |
| Total | 51 | 12 | 39 | 24 | 27 | 28 | 23 |
| $\chi^2$ | | 11.6992 | | 4.3624 | | 1.5485 | |
| p | | <.005 | | NS | | NS | |

See text for definition of categories.
NS — not significant.

*While Awake*. The A:B ratio of SaO2 of each group while awake is shown in Fig 18. There was no significant difference with regard to SaO2 among the three groups of patients. But in young babies SaO2 was unstable, and when they were put on the bed they began to cry almost immediately. They stopped crying when they were held in someone's arms. Their SaO2 was stable when they were lying on the bed in a prone position with the neck extended.

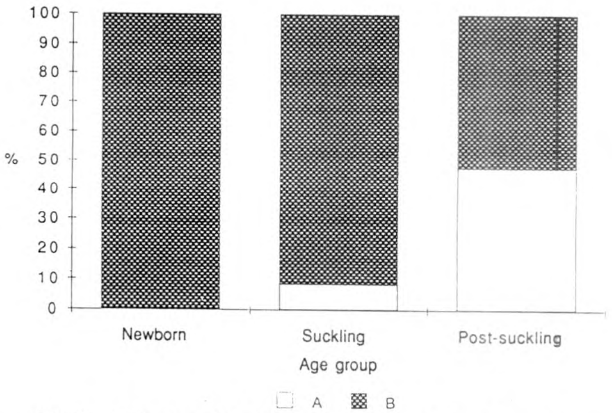

Fig 10. A:B ratio of SaO2 in each group during sleep. See Fig 9 for definitions.

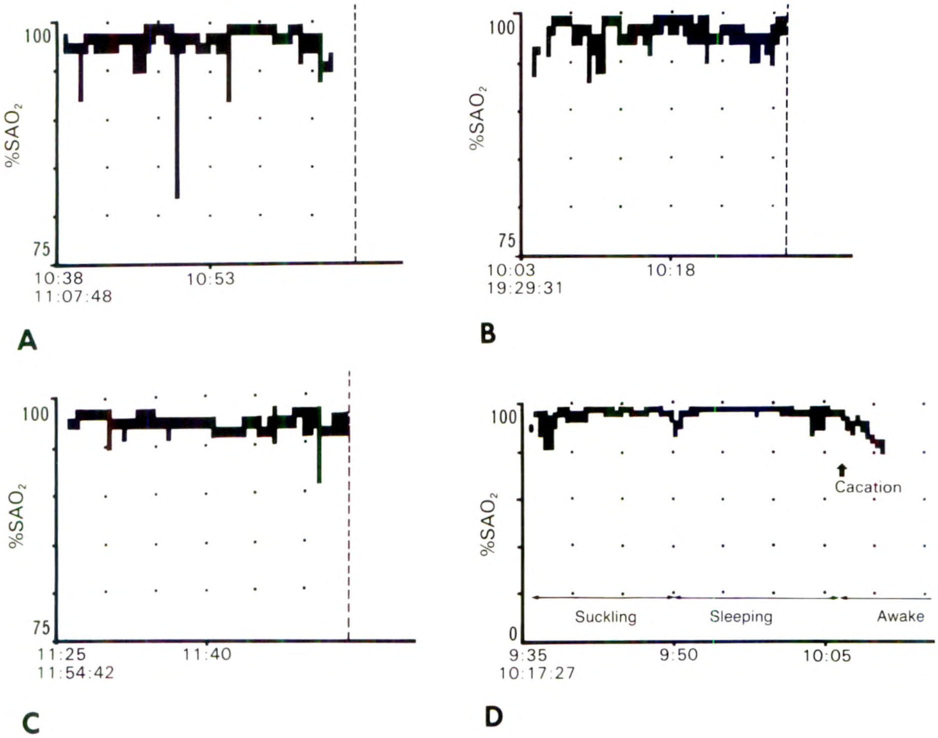

Fig 11. (Case 15) Preoperative and postoperative SaO2 patterns in 15-week-old boy during sleep, during suckling, and while awake. Preoperative SaO2 is unstable in all states, but postoperative SaO2 is higher and stable. A) Sleep. B) Suckling. C) Awake. D) Suckling and sleeping just after operation. Patient awoke on cacation.

After the operation, in 43 of 45 patients SaO2 was 99% the first day and sometimes 98% or 97% during sleep (Figs 11D and 12B). In 2 patients, SaO2 was 99% most of the time, occasionally decreasing to levels below 95%; but 3 weeks later their SaO2 was stable at 99%. The infants had no breathing difficulties after the operation, and the pulse rate decreased in those babies who had increased pulse rates during sucklings before the operation (Fig 17). A decrease in pulse rate was also observed during sleep and while awake. Suckling time became less in all babies. After the operation 95.6% of the patients were classified type A while awake — the same as during sleep (Fig 9).

### SKIN AND HAIR

The distribution of skin characteristics observed on the first visit is shown in Table 1 and Fig 19A and the distribution of skin characteristics by age is shown in Table 5. The statistical analysis revealed significant differences regarding skin signs between these groups ($p < .01$). Moreover, there were no significant differences with regard to marbled and cyanotic skin; however, there were differences between our study population and normal groups by Student's $t$ test ($p < .01$). The distribution of hair characteristics observed on the first visit is shown in Table 1 and Fig 19B, and that of hair characteristics by age group is shown in Table 6. Regarding the hair signs, it is noteworthy that in patients with piloerection this sign was more notable in the occipitoparietal region than in the frontal and temporoparietal regions. The distribution of types of skin and hair by SaO2 during sleep, during suckling, and while awake is shown in Table 7. There was a direct relationship between skin signs and SaO2 ($p < .05$), but not between SaO2 and hair signs (Table 8).

Cyanosis disappeared just after the operation, and the marbled color gradually disappeared or

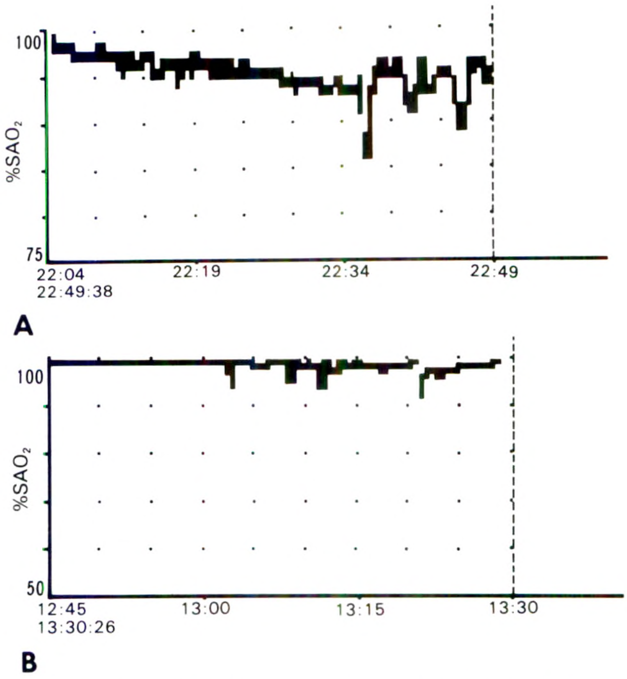

Fig 12. (Case 37) SaO2 during sleep in 18-week-old girl. A) Preoperative. About 1 hour after she fell asleep, her SaO2 began to drop, and finally she awoke. She had chief complaint of sleep apnea, but also had breaks in respiration of 1 or 2 seconds and harsh respiratory sounds. B) Postoperative. About 1 hour after she fell asleep, SaO2 was stable. Breaks in respiration and harsh respiratory sounds ceased also.

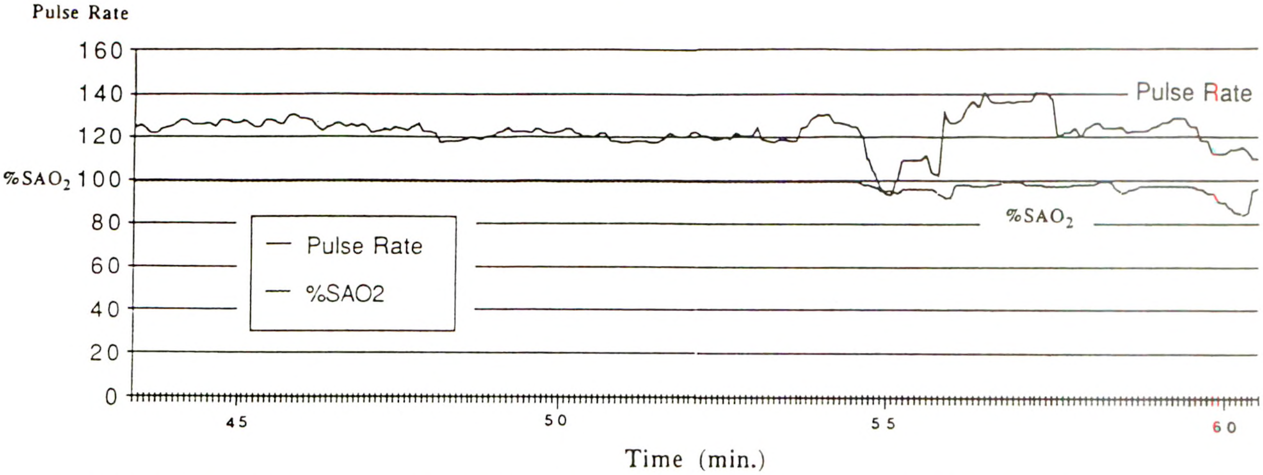

Fig 13. (Case 49) Preoperative changes in pulse rate and SaO2 during sleep in 54-week-old boy. His SaO2 was stable at 99% and pulse rate was 120 until about 54 minutes after he fell asleep. Then his pulse rate suddenly rose, then fell, and his SaO2 also decreased. Finally he was awakened with movements.

faded away in the weeks following the operation. Changes in hair signs were not so striking as those of the skin; however, according to their mothers' observations, the babies' hair did not stick to their sheets, caps, or towels after the operation. Piloerection at the frontal and temporoparietal areas also began to disappear. But some babies even 2 or 3 months after the operation still had piloerection in the occipital region.

### OTHER SYMPTOMS

Besides dyspnea, suckling problems, and the skin and hair signs described above, we observed several other symptoms, such as dark forehead, dark color around the lips, scanty eyebrows and eyelashes, frowning expression, and retarded development of the mandible and temporal muscles, which resulted in hollowed fronto-orbitotemporal regions. Moreover, swelling around the palpebrae, harsh respiratory sounds, cornifications of the mucous membrane in the middle of the dorsum linguae (Fig 20A), high hard palate, hypertrophy in the lower part of the cheeks, slight retraction of the chest, pigmentation of the skin by the nail wall (Fig 20B), and too fast or too slow growth were observed.

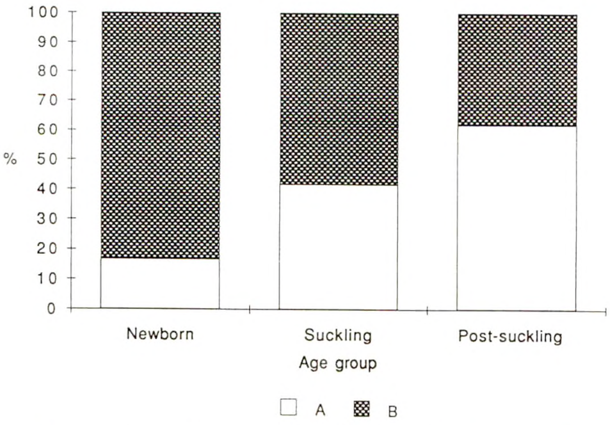

Fig 14. A:B ratio of SaO2 in each group during suckling. See Fig 9 for definitions.

These babies cried hard, snored, yawned frequently, had weak muscle tone and cold extremities, and were emotionally unstable. They had thin fingers and could not hold or could only weakly hold the experimenter's forefinger. They had *dakiguse*, ie, they wanted to be always in someone's arms and did not stop crying until they were held by somebody. They were very inactive and could not gaze at objects. It was difficult for them to fall asleep and they awoke very easily. They did not play alone and had the habit of finger-sucking, they choked and spit up milk frequently, and they had *hitomishili*, ie, they seemed to be strongly afraid of strangers. However, in spite of all these signs, pediatricians had told their mothers the babies were healthy.

After the operation, we noted that most of the signs described above had disappeared. That is, the babies were livelier and looked healthier. The expression on their faces was peaceful. They could gaze at and follow objects, and the palpebral swelling disappeared. They became active, turned

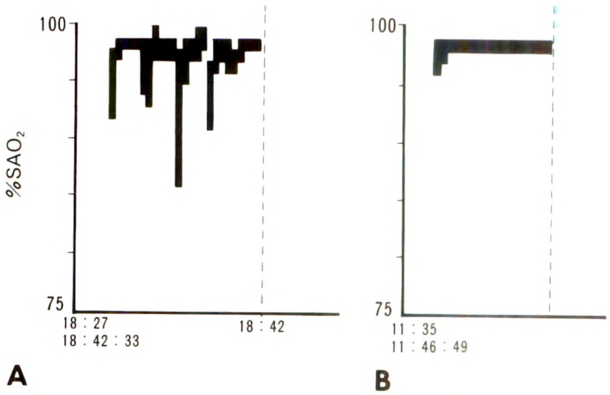

Fig 15. (Case 39) Changes in SaO2 in 45-week-old girl during suckling of 100 mL of milk. A) Preoperative. As soon as she began to suck milk, SaO2 decreased. When it decreased most, she began to cry and bent back her head. She did not finish all of her milk. B) Postoperative. SaO2 was stable. She gulped 100 mL of milk and her SaO2 was stable. Suckling time was shortened also.

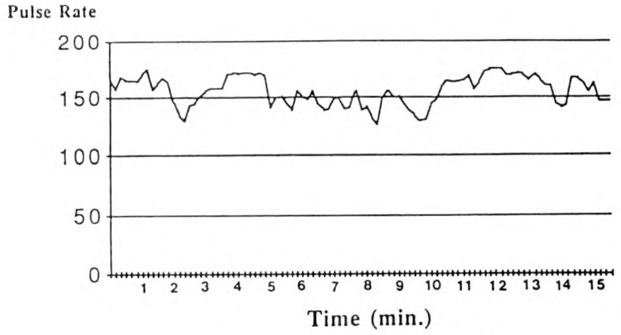

Fig 16. (Case 34) Preoperative changes in pulse rate in 11-week-old boy during suckling. His SaO2 was stable at 97% or 98% while awake, but when he started sucking it rose to 99%. With sucking his pulse rate increased to 170 or more, and when his pulse rate increased he stopped sucking. He started suckling again only when his pulse rate went back to normal. He fell asleep with his mother's nipple in his mouth.

around in their beds, played alone, clasped things, and explored their bodies with their hands. A baby in whom the diagnosis had been central muscle atony could even walk by himself the next day after the operation. The babies stopped crying before or after falling asleep and slept well. Their harsh respiratory sounds disappeared. The first night after the operation their abnormal respiratory sounds ceased to the extent that some of the mothers went to look at them several times while the babies were asleep because they thought the babies had died. Their voices became clear and loud. Several weeks after the operation we noticed that the cornifications of the dorsum linguae had disappeared and their eyebrows and eyelashes had turned thicker. Mothers said that it was easier for them to take care of their babies after the operation, that now the babies laughed more frequently, and that somehow they felt more fond of their babies.

## DISCUSSION

It has been observed that ankyloglossia babies have suckling difficulties and other symptoms, such as a frowning expression, a dark forehead, a whitish tongue, adducted feet, and hard crying. But causes of these symptoms were thought to be related to their mothers' milk[10,11] (also Suzuki and Katagili, unpublished observations, 1989). It became clear in our observations that ankyloglossia accompanies deviation of the epiglottis and larynx. The relationship between ankyloglossia and respiration had been missed. We will discuss ankyloglossia and displacement of the epiglottis and larynx, and the relationship between this disease and respiration and the other symptoms observed. Finally, we will discuss the relationship between this disease and SIDS.

### ANKYLOGLOSSIA

According to our observations, although there is an improvement regarding the mobility of the tongue as patients grow older, ankyloglossia itself does not change. Therefore, the degree of mobility of the tongue does not reflect the real state of ankyloglossia.

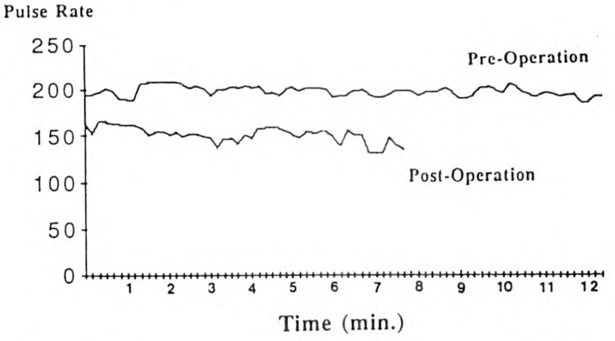

Fig 17. (Case 33) Changes in pulse rate in 15-week-old boy before and after operation. Before operation, he finished suckling with increased pulse rate. After operation, both his pulse rate and feeding time were decreased. Decrease of pulse rate was observed not only in suckling, but also during sleeping and while awake.

When examining a patient, experimenters should pull the tip of the tongue up to determine the position of the frenulum and examine the base of the tongue; otherwise, if they limit themselves to asking the patient to move the tongue and check its mobility only, they will miss those cases of ankyloglossia accompanied by deviation of the tongue. Also, most classifications of ankyloglossia have been done taking into account the degree of attachment of the frenulum alone[8,18-22] without considering the origin of the free portion of the tongue in relation to the floor of the mouth. On the basis of the system we propose here, those cases classified as F3 and/or B2 or B3 were diagnosed as ankyloglossia. Of the reported cases, by the frenulum alone only 17 cases (33.3%) out of 51 would be diagnosed as ankyloglossia. By the tongue base, 43 cases (84%) could be diagnosed as ankyloglossia. These results (Fig 6B,C) demonstrate that it would have been impossible to achieve the correct diagnosis of ankyloglossia solely on the basis of the frenulum. Moreover, some of the patients who had been operated on before being referred to our clinic showed very little improvement after that first frenotomy alone, and we had to op-

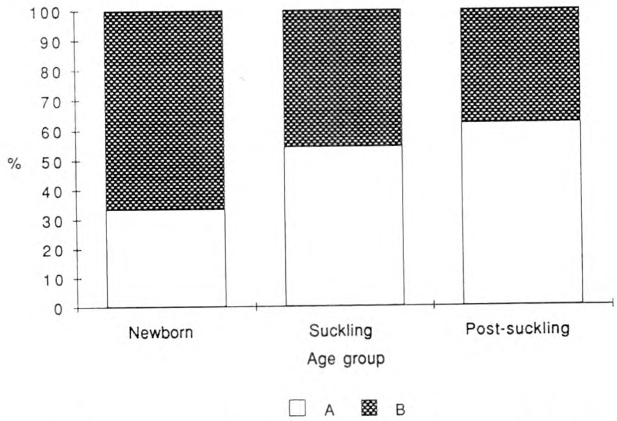

Fig 18. A:B ratio of SaO2 in each group while awake. See Fig 9 for definitions.

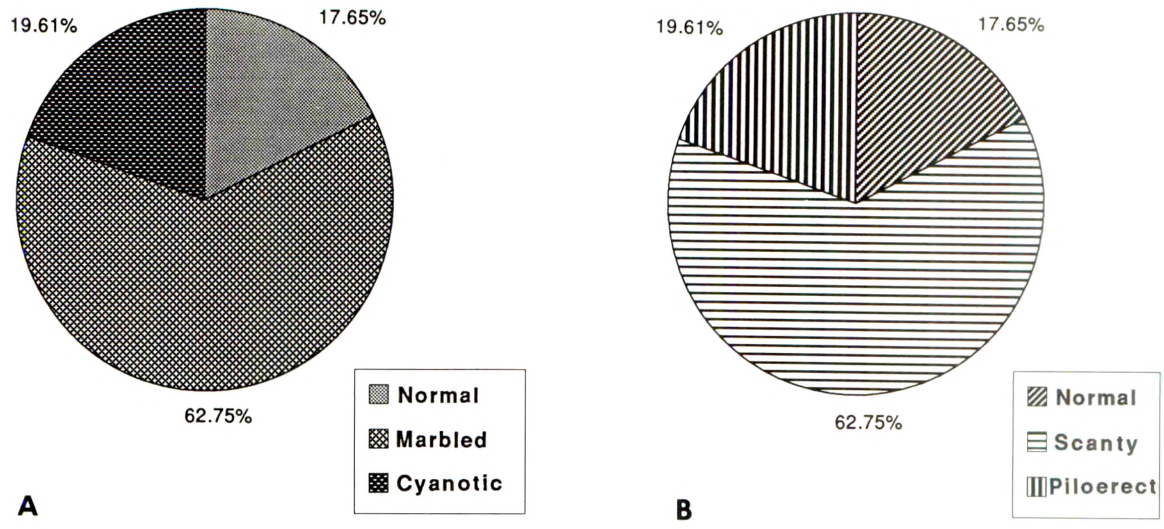

Fig 19. Distribution of A) skin and B) hair characteristics.

erate on them once more. Satisfactory results were obtained after the second operation, which corrected the tongue, epiglottis, and larynx as described above.

EPIGLOTTIS AND LARYNX

Displacement of the larynx was observed in 84% of the patients. Displacement of the epiglottis was in close correlation with that of the base of the tongue. After the operation the epiglottis was in its correct position in all the patients, and the larynx in 87% of them. These results demonstrate that ankyloglossia is accompanied by displacement of the tongue and of the epiglottis and larynx.

In normal newborn babies the epiglottis and the larynx stand upright toward the nasopharynx. In newborns, both conjugate with the nasopharynx during sucklings,[23] so the infants can breathe while feeding. The arytenoid cartilages in normal infants are located in an anterior position with regard to those of adults, and the movements of the cricoarytenoid joints are mainly horizontal.[24,25] However, in our patients we observed vertical movements, too; the plicae aryepiglottica, the tubercula corniculum, and the tubercula cuneiform moved vertically over to the vocal folds, partially covering them during phonation. However, after the operation these movements were reduced and the patients' voices sounded loud and clear. The structures might work as a muffler. Another factor involved was probably the improvement of the resonance of the vocal folds, for a stream of air hitting them at a right angle made them vibrate more effectively than before the operation.

The infants' harsh respiratory noises disappeared after the operation. We think that harsh respiratory sounds existed in relation to the deviation of the larynx and incomplete abduction of the vocal folds — probably because the deviation of the larynx interfered with the movements of the posterior cricoarytenoid muscles and/or the cricoarytenoid joints.

Since the epiglottis was also deviated toward the radix linguae, there was no full conjugation of the nasopharynx with the epiglottis and larynx. Consequently, these babies had difficulties and choking during sucklings. The rapid decrease in SaO2 was probably due to a reflexive defensive closure of the larynx.[26-28]

After the operation the position of the epiglottis and the larynx was corrected and choking during sucklings disappeared. Therefore, the operation served two purposes: to obtain an increased volume of the free portion of the tongue and to correct the deviations of the epiglottis and larynx.

During induction of general anesthesia, we observed closure of the vocal cords in some patients. The vocal cords did not open even when SaO2 decreased to levels below 40%. All of the patients were 14 weeks old or younger and their SaO2 was unstable during sleep. We think that these patients' laryngeal closure occurred very easily and it was difficult for them to respond to the hypoxia.[29,30] In three patients we detected vocal cord nodules that no doubt

TABLE 5. SKIN CHARACTERISTICS BY AGE GROUP

| | *Normal* | *Marbled* | *Cyanotic* |
|---|---|---|---|
| Newborn | 1 | 3 | 2 |
| Suckling | 0 | 20 | 4 |
| Post-suckling | 8 | 9 | 4 |
| Total | 9 | 32 | 10 |

$\chi^2 = 35.8220$; $p < .01$.

TABLE 6. HAIR CHARACTERISTICS BY AGE GROUP

| | *Normal* | *Scanty* | *Piloerect* |
|---|---|---|---|
| Newborn | 1 | 4 | 1 |
| Suckling | 2 | 10 | 12 |
| Post-suckling | 5 | 5 | 11 |
| Total | 8 | 19 | 24 |

$\chi^2 = 6.9060$ (not significant).

TABLE 7. DISTRIBUTION OF TYPES OF SKIN AND HAIR BY ARTERIAL OXYGEN PERCENT SATURATION DURING SLEEP, SUCKLING, AND WHILE AWAKE

| | | *Asleep* | | *Suckling* | | *Awake* | |
|---|---|---|---|---|---|---|---|
| | *Cases* | *A* | *B* | *A* | *B* | *A* | *B* |
| Skin | | | | | | | |
| Normal | 9 | 6 | 3 | 7 | 2 | 8 | 1 |
| Marbled | 32 | 5 | 27 | 11 | 21 | 17 | 15 |
| Cyanotic | 10 | 1 | 9 | 6 | 4 | 3 | 7 |
| Total | 51 | 12 | 39 | 24 | 27 | 28 | 23 |
| Hair | | | | | | | |
| Normal | 8 | 3 | 5 | 5 | 3 | 5 | 3 |
| Scanty | 19 | 5 | 14 | 8 | 11 | 12 | 7 |
| Piloerection | 24 | 4 | 20 | 11 | 13 | 11 | 13 |
| Total | 51 | 12 | 39 | 24 | 27 | 28 | 23 |

See text for definition of categories.

TABLE 8. STATISTICAL RELATIONSHIP BETWEEN SKIN AND HAIR SIGNS AND ARTERIAL OXYGEN PERCENT SATURATION

| | *Asleep* | *Suckling* | *Awake* |
|---|---|---|---|
| Skin | | | |
| $\chi^2$ | 11.4362 | 6.1476 | 11.4362 |
| p | .0462 | .0343 | .0033 |
| Significance level | $p<.05$ | $p<.05$ | $p<.005$ |
| Hair | | | |
| $\chi^2$ | 1.578 | 0.9672 | 1.5067 |
| p | .4543 | .6166 | .4708 |
| Significance level | NS | NS | NS |

NS — not significant.

were caused by excessive crying. Three months after the operation these nodules had disappeared.

We observed also that although icterus neonatorum had already disappeared in their skin, jaundice was observed in the laryngeal membranes. Perhaps icterus neonatorum presents last in the larynx. Narrowing of the choanae was observed in 24% of the patients. Although we did not find a relationship between the narrowing of the choanae and this congenital disease, there is a possibility that this disease accompanies choanal narrowing at a high rate.

MOVEMENTS DURING SUCKLING

Normal suckling movements involve biting, sucking, mastication, and swallowing. However, in patients with ankyloglossia with displacement of the epiglottis and larynx, these movements are reduced to sucking and swallowing[10,11] (also Suzuki and Katagili, unpublished observations, 1989).

To examine the movements during suckling the senior author (S.M.) put his little finger in the babies' mouths; normally, babies would wrap the finger with the tip of the tongue and bite rhythmically with their gums and they would suck the finger. Their tongues are soft. But these patients neither wrapped nor bit the finger. They just sucked the finger by pressing it with the dorsum of the tongue against the hard palate. Their dorsa linguae were hard also. It is very likely that the high hard palate and the cornification of the dorsum linguae we observed in these babies were due to their peculiar suckling pattern. Moreover, it is worth mentioning that many of their mothers had deformed or wounded nipples, probably because of this abnormal suckling pattern. The same can be said of the retarded development of the mandible and temporal muscles and the hypertrophy of the lower part of the cheek.

OXYGEN SATURATION RATE

There was a statistically significant inverse relationship between age and the level of SaO2 during sleep. The SaO2 was quite unstable in newborn babies and young infants; in fact, all the patients in whom SaO2 dropped below the 85% level were babies under 15 weeks of age. These babies were at a great risk of falling into a state of hypoxia. Moreover, they showed a limited response to hypoxia. Therefore, it is not exaggerating when we say that the life of a baby with this disease is in danger during sleep.

As the babies grew older SaO2 became more stable; there were patients who became very lively when they were about 4 months old. We think that as they grow older, their muscles become stronger and the elasticity of the oral tissues increases. Thus, the negative effects of this disease probably subside by 4 months or more.

After the operation, the basal value of SaO2 rose to 99% in all the patients, and SaO2 remained stable during sleep. We concluded that the state of hypoxia observed in these patients during sleep was due to ankyloglossia and the concomitant deviation of the epiglottis and larynx.

In some patients we detected hypoxia even when they were awake, and SaO2 was especially low when they were in bed lying on their backs. When SaO2 was low they started to cry. It seems that in the supine position the resistance of the respiratory airway increases. The babies slept well with the neck extended while being cuddled in someone's arms. This position might decrease the airway resistance. Apparently, the babies developed *dakiguse*, or a cuddle habit, because of an uncomfortable increase of the airway resistance. We think that babies cry to get enough oxygen and that *dakiguse* is closely related to this anomaly.

There are several reports in the literature about babies with ankyloglossia who have suckling problems. Most authors reported that these babies would suddenly stop sucking and push aside their mothers' nipples, or they would suddenly start crying during sucklings, or they would show displeasure at the sight of their mothers' breasts, turning their face in the opposite direction. The explanation given for this abnormal behavior was that the babies could not wrap the nipple with the free portion of their tongue.[3,8-11] According to our observations, as demonstrated here, there was always a drop in SaO2 at the time they suddenly stopped sucking or when

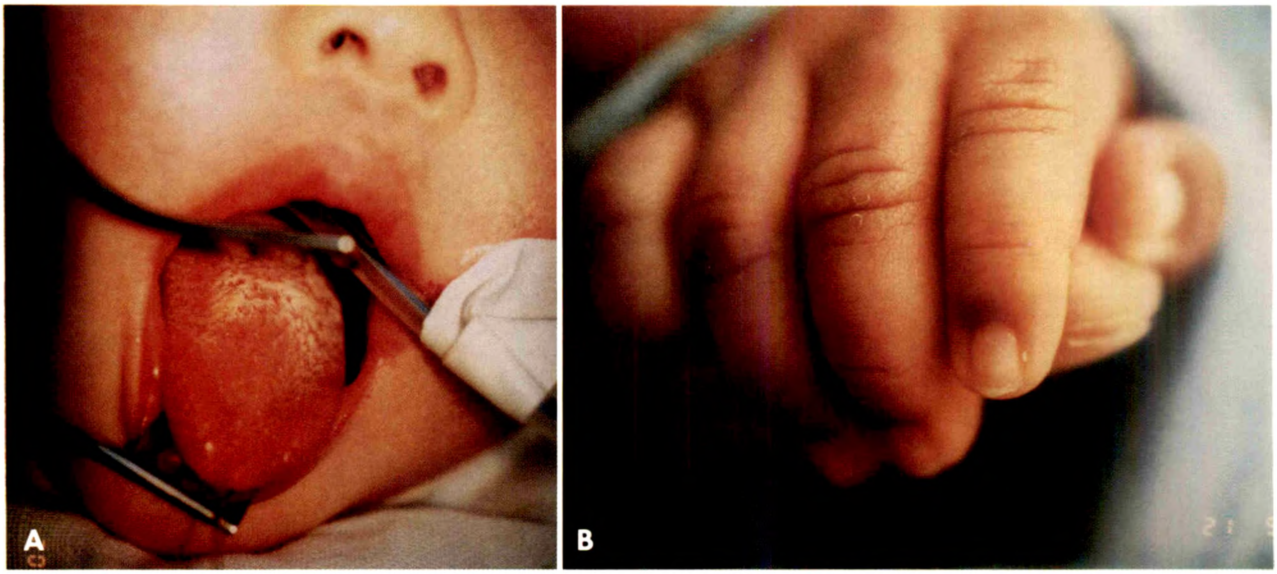

Fig 20. Other symptoms. A) Cornification of dorsum linguae. It is white and harder than normal when palpated with finger. B) Pigmentation of skin of nail wall. This was present in all patients.

they suddenly began crying — probably because there was a reflexive closure of the larynx at that very moment.

Some of the patients in our study would stop sucking, rest for a while, and then continue sucking. When they stopped sucking their pulse rate was very high but their $SaO_2$ was about 99%. They might hyperventilate. These babies usually fell asleep during sucklings, and we think that they were under strong stress due to a respiratory and circulatory conflict while they were feeding themselves. Therefore, it was only natural for them to feel tired during sucklings and fall asleep out of exhaustion. Moreover, we observed that these babies, especially post-suckling babies, were emotionally unstable — perhaps because of the stress they were subjected to while they were trying to feed themselves. The suckling movements gradually normalized after the operation in all the patients, and younger babies started to suckle with a normal rhythm sooner than the older ones. They neither choked nor fell asleep during sucklings, and their pulse rate decreased to normal levels not only during sucklings but also while they were awake or sleeping. A notorious increase of the babies' suckling abilities after frenotomy has been reported by several other investigators in the past[3,7,8,10,11,31,32] (also unpublished observations, Suzuki and Katagili, 1989, and Yoshimi and Ajimoto, 1989). We think that the increase they reported was due not only to an increased mobility of the tongue but also to an improvement of their respiratory and circulatory functions.

## TONGUE, LARYNX, EPIGLOTTIS, AND RESPIRATION

According to Comroe,[33] the resistance of bronchi under 2 mm in diameter is 10%, that of the nose and oral cavity is 30% to 50%, and that of the larynx is 25%. The carbon dioxide response of the genioglossus muscle is in proportion to that of the diaphragm muscle.[34,35] The posterior cricoarytenoid muscles discharge in synchrony with that of the diaphragm.[26,36] The ala nasi muscles also act in concert with the posterior cricoarytenoid muscles.[37] That is, the ala nasi muscles, genioglossal muscles, and posterior cricoarytenoid muscles are tonic during inspirations. Activities of the intrinsic muscles of the larynx are also important during expirations.[38] The activities of these muscles are elevated in supine positions, but in rapid eye movement sleep their activities greatly decrease.[39-44] Togawa et al[45] observed hypoxia with obstructive sleep apnea in infants during rapid eye movement sleep. In dogs, hypoxia causes awakening from sleep. We think that as seen in infants with obstructive sleep apnea and dogs, the reported patients awoke because of hypoxia during rapid eye movement sleep. They may be drowsy and they frequently yawn during the daytime.

Dropping of the radix linguae has been reported in patients with nocturnal sleep apnea.[35,39,40] But we cannot think that the dyspnea of this disease is caused by dropping of the radix linguae, for the tongue is rather in a forward position in the patients with congenital ankyloglossia. And the operation for this disease rotates the tongue down and back. The epiglottis and the larynx also move down and back. After the operation the dyspnea disappears.

The authors deduced dyspnea in this disease from the following observations: 1) an increase of upper airway resistance caused by displacement and less abduction of the larynx, 2) incomplete conjugation of the nose and the epiglottis and larynx, 3) displacements of the larynx, tongue, and epiglottis that decrease activities of respiration, and 4) consequent decreased elasticity of the lung. The authors imagine that the patients had central lesions caused by hypoxia, but cannot deduce that dyspnea was produced by direct central lesions caused by these congenital anomalies.

### SKIN AND HAIR

Abnormal signs of the skin and hair were found in 80% and 84% of the patients, respectively. The high frequency of these signs in babies with this disease suggests a close relationship between this anomaly and the skin and hair signs.

A significant direct relationship was observed between SaO2 and skin signs. We can say that the abnormal skin signs are related to the hypoxia state. Usually cyanosis is observed when the blood PO2 drops below 5 g/dL. Under normal conditions cyanosis appears in the extremities and the nails. Marbled skin can also be seen as a response to cold, and it is more prominent when the patient is debilitated. It is caused by abnormal ectasia of capillaries. However, its pathophysiology is unknown.[46] But in patients with this congenital disease the presence of cyanosis or marbled skin is related to their hypoxia state. There was no significant relationship between the presence of cyanosis and marbled skin. But our impression is that patients with cyanosis were less vigorous than those with marbled skin. And the skin of the former is colder than that of the latter.

Although no significant relationship was observed between the presence of abnormal hair signs and SaO2, after the operations the hair became thicker in those babies who had scanty hair before the operation, and piloerection tended to disappear. We think that as the changes of hair required weeks, there may be a time lag between the two.

### OTHER SYMPTOMS

As for the other symptoms we observed in these patients, which may be easily and erroneously taken as nonspecific, all disappeared as soon as SaO2 became normal, except for the thin eyebrows and eyelashes, which changed later in time. It can be said that the following signs or symptoms were due to hypoxia: dark foreheads, darkness around the lips and of the lips themselves, frowning, slightly swollen palpebrae, hard crying, decreased muscle tone, yawning, cold extremities, inactivity, difficulty in gazing at objects, and light sleep. We think that ankyloglossia itself caused such symptoms as underdevelopment of the mandible and temporal muscles, cornifications of the mucous membrane of the dorsum linguae, swelling in the lower part of the cheeks, and too fast or too slow development. Owing to displacement of the epiglottis and larynx, choking and spitting up occurred easily. A light retraction of the chest and harsh respiratory sounds might also be caused by these displacements.

We think that other signs, ie, sucking on their fingers, their strong anxiety about strangers, their emotional instability, and their *dakiguse* were probably related to the dyspnea and their respiratory as well as circulatory distress. We observed no infants who were operated on before 3 months who had anxiety about strangers. We think that pigmentations of the skin on the nail bed could have been caused by chronic hypoxia.

### RELATIONSHIP BETWEEN ANKYLOGLOSSIA AND SUDDEN INFANT DEATH SYNDROME

According to the data found in the literature, the following are some of the symptoms that have been observed, prior to their death, in babies who fell victim to SIDS. These babies cried hard, they were breathless and exhausted during sucklings, their reaction to stimuli from the environment was less intense than in other babies, their growth rate was rather slow, and their pulse rate was high.[15,16,19] All the reported signs are related to a chronic state of hypoxia.[47-49] Finally, it is common knowledge that most victims of SIDS were babies 2 to 3 months old and that they had a history of near-miss episodes.[50]

The symptoms and epidemiologic characteristics of both SIDS and ankyloglossia, as reported here, are so strikingly similar that it is difficult not to suspect a similar pathogenesis. Mirchandani et al[51] reported that in every epidemiologic study SIDS was less prevalent in breast-fed babies than in bottle-fed babies. This fact suggests that SIDS babies probably had difficulties in suckling and therefore had been bottle-fed.

There was one case of near-miss SIDS among our cases reported. In our experience, among 181 patients with ankyloglossia we had three near-miss cases.[52,53] Moreover, there is a report of a SIDS victim whose brother had undergone frenotomy due to ankyloglossia (Suzuki and Katagili, unpublished observations, 1989).

According to our review of the literature, this is the first study in which a classification and definition of ankyloglossia from a physiologic point of view has been attempted. In this study we established the relationship existing between ankyloglossia and deviations of the epiglottis and larynx. The implications these anatomic abnormalities have for the respiratory function were also demonstrated for the first time. Moreover, on the basis of the data available to us, we can say that almost no or very little consideration has been paid to this anomaly, which has an autosomal dominant character.[9]

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ACKNOWLEDGMENTS — The authors thank Y. Murakami, MD (Kyoto Huritu Medical School, Kyoto, Japan), for his advice during preparation of this work. The authors thank P. Lopetegui, DDS (Tokyo Tanabe Pharmaceutical Co, Ltd, Tokyo, Japan), for assistance in preparing the English-language manuscript.

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SUPPLEMENT 154 — SEPTEMBER 1991
Volume 100, Number 9, Part 2

12/11/92

UCM

# WORKSHOP ON THE ROLE OF ANAEROBIC BACTERIA IN INFECTIONS OF THE UPPER RESPIRATORY TRACT–HEAD AND NECK

Editors
CHARLES D. BLUESTONE, MD
JEROME O. KLEIN, MD

Associate Editor
MARY D. SCHEETZ, MLS

ANNALS
OF OTOLOGY,
RHINOLOGY &
LARYNGOLOGY

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Additional copies of this publication are available from Charles D. Bluestone, MD, Dept of Pediatric Otolaryngology, Children's Hospital of Pittsburgh, 3705 Fifth Ave at DeSoto St, Pittsburgh, PA 15213-2583, or may be purchased from Annals Publishing Company, 4507 Laclede Ave, St Louis, MO 63108.

PUBLICATION OF THIS SUPPLEMENT
WAS MADE POSSIBLE BY
AN EDUCATIONAL GRANT FROM
SMITHKLINE BEECHAM PHARMACEUTICALS,
PHILADELPHIA, PENNSYLVANIA.

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# PARTICIPANTS

Ann Sullivan Baker, MD
Professor of Medicine
Harvard Medical School
Director, Infectious Disease Unit
Massachusetts Eye and Ear Infirmary
Physician, Infectious Disease Unit
Massachusetts General Hospital
Boston, Massachusetts

John G. Bartlett, MD
Chief, Division of Infectious Diseases
Johns Hopkins Hospital
Baltimore, Maryland

Charles D. Bluestone, MD, Co-moderator
Professor of Otolaryngology
University of Pittsburgh School of Medicine
Director, Department of Pediatric Otolaryngology
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Itzhak Brook, MD, MSc
Professor of Pediatrics and Surgery
Uniformed Services University
of the Health Sciences
Washington, DC

Sydney M. Finegold, MD
Associate Chief of Staff for Research and
Development
West Los Angeles Veterans Administration
Medical Center
Los Angeles, California

Robert S. Fulghum, PhD
Professor
Department of Microbiology and Immunology
School of Medicine
East Carolina University
Greenville, North Carolina

Sherwood L. Gorbach, MD
Professor of Community Health and Medicine
Tufts University School of Medicine
Boston, Massachusetts

Walter J. Loesche, DMD, PhD
Professor of Dentistry and Microbiology
University of Michigan School of Dentistry
and School of Medicine
Ann Arbor, Michigan

Jonas T. Johnson, MD
Professor and Vice Chairman
Department of Otolaryngology
University of Pittsburgh School of Medicine
Eye and Ear Institute
Pittsburgh, Pennsylvania

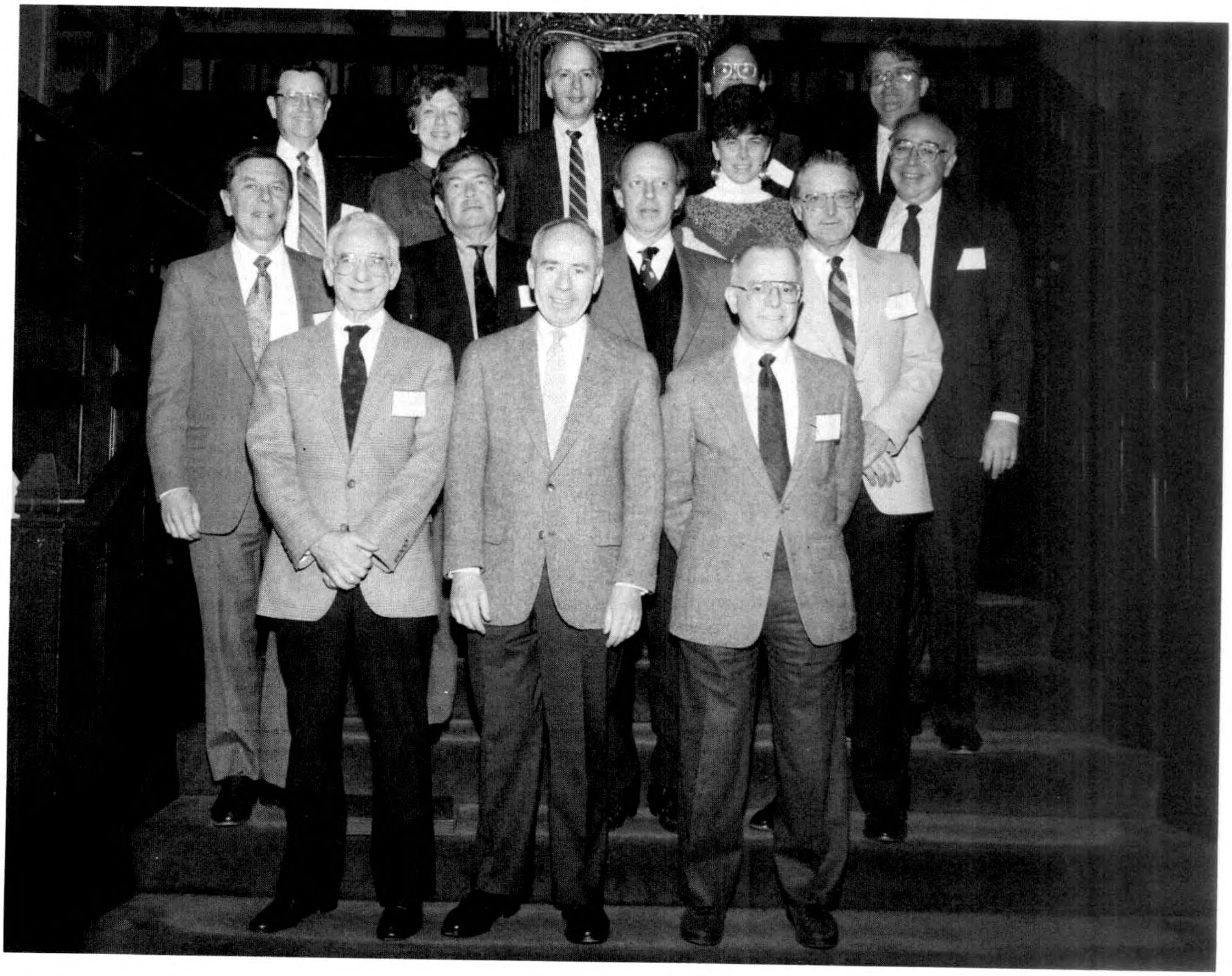
Jerome O. Klein, MD, Co-moderator
Professor of Pediatrics
Boston University School of Medicine
Director, Division of Pediatric Infectious Diseases
Maxwell Finland Laboratory for Infectious Disease
Boston City Hospital
Boston, Massachusetts

Jack L. Paradise, MD
Professor of Pediatrics
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Clyde Thornsberry, PhD
Institutes for Microbiology Research
and Department of Pathology
Vanderbilt University
Nashville, Tennessee

Ellen R. Wald, MD
Professor of Pediatrics
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Victor L. Yu, MD
Professor of Medicine
University of Pittsburgh School of Medicine
Division of Infectious Diseases
Chief, Infectious Disease Section
Veterans Administration Medical Center
Pittsburgh, Pennsylvania



WORKSHOP PARTICIPANTS

*Front Row*: Charles D. Bluestone, Jack L. Paradise, Jerome O. Klein.

*Second Row*: Walter J. Loesche, Clyde Thornsberry, John G. Bartlett, Ellen R. Wald, Sydney M. Finegold, Sherwood L. Gorbach.

*Third Row*: Robert S. Fulghum, Ann Sullivan Baker, Itzhak Brook, Victor L. Yu, Jonas T. Johnson.

# INTRODUCTION: GOALS OF THE WORKSHOP

The Workshop on the Role of Anaerobic Bacteria in Infections of the Upper Respiratory Tract–Head and Neck was held in Pittsburgh, Pennsylvania, on December 15-16, 1988, as part of an ongoing series sponsored by the Otitis Media Research Center of the Children's Hospital of Pittsburgh.[1-8] The need for such a workshop is evident for the following reasons. 1) There is a great deal of controversy among experts as to the incidence of anaerobic bacteria in infections of the upper respiratory tract–head and neck. 2) There is uncertainty about the most effective methods to collect specimens, technique of transport, and laboratory culture and susceptibility technique. 3) Questions have been raised concerning pathogenicity of anaerobes and the possible role of these organisms in the cause of infections in this area. 4) Controversy exists over whether or not antimicrobial therapy should be administered on an empiric basis to be effective against possible anaerobic bacteria in certain infections in these areas.

Related to these controversial questions, the workshop had the following goals: 1) determine our state of knowledge of the incidence of anaerobic bacteria in infections of the upper respiratory tract–head and neck; 2) reach a consensus on the possible role of anaerobes in these infections; 3) reach a consensus on recommendations for treatment of infections in this area related to the incidence of anaerobic bacteria; 4) recommend future research direction for not only infections of the middle ear and mastoid, but for other infections of the upper respiratory tract–head and neck; and 5) disseminate this information to the health care community.

We invited leading experts in this country who have a deep interest and vast experience in this area to share their knowledge with us, prepare a manuscript for this supplement, deliberate the controversial aspects, and arrive at a consensus related to these questions and recommend future research directions.

We are indebted to SmithKline Beecham Pharmaceuticals for an educational grant to share in the financial support for the workshop and for this publication of the proceedings.

Charles D. Bluestone, MD
Jerome O. Klein, MD

# STATE OF KNOWLEDGE

# ANTIMICROBIAL SUSCEPTIBILITY TESTING OF ANAEROBIC BACTERIA: REVIEW, COMMENTS, AND OPINIONS

CLYDE THORNSBERRY, PHD

## INTRODUCTION

The discovery of penicillin resulted from Fleming's fortuitous recognition that some substance — later to be named penicillin — produced by a mold had diffused into the medium on which it was growing and was inhibiting staphylococci also growing on the agar plate. Thus an antimicrobial susceptibility test had been performed for penicillin against the staphylococci. Within a few years a method for determining the minimal inhibitory concentration (MIC) of penicillin was described.[9] In the next five decades, several methods would be described for performing antimicrobial susceptibility tests and much effort would be directed toward the standardization of some of these methods. The major emphasis during these "antibiotic years," however, has been on susceptibility methods to be used for testing organisms that grow aerobically — principally staphylococci, Enterobacteriaceae, and *Pseudomonas aeruginosa*.

Thus, antimicrobial susceptibility testing of aerobic and facultatively anaerobic bacteria has been a routine procedure in most clinical microbiology laboratories since the 1940s or 1950s — but not of anaerobes. It is only very recently that susceptibility testing of anaerobes could be considered a routine procedure. Even now, it is more likely to be only a special test or not done at all in many laboratories, even though they do susceptibility tests routinely on nonanaerobic bacteria. This is a result of the failure, until recent years, of many laboratories to isolate anaerobic bacteria from clinical material. Thus, the primary sources of information concerning the susceptibility of anaerobes to antimicrobial agents have come from a few research laboratories, whose data were usually developed by using different methods. As more clinical laboratories began to isolate anaerobes, the demand for routine testing increased. In recognition of this demand, the National Committee for Clinical Laboratory Standards (NCCLS) established a subcommittee to study the problem and, in 1979, published a proposed standard for antimicrobial susceptibility of anaerobic bacteria; it became an approved standard in 1985,[10] and a recently revised edition was published.[11] The standard method is an agar dilution technique — a technique that can yield accurate and reproducible results but is generally too inconvenient for routine use in a clinical laboratory. Therefore, the NCCLS standard became, for the most part, a method to which alternative, more convenient methods could be compared. Again recognizing the problem, the NCCLS published a guideline that described various alternative methods that could be used to test anaerobic bacteria.[12] In the 1991 revised standard,[11] these two documents were combined, resulting in standard descriptions for several methods.

In spite of these efforts, problems concerning antimicrobial susceptibility tests and their role in the therapy of anaerobic infections have continued and have again been recognized by the NCCLS.[13] In this report, the susceptibility methods and these problems will be described and discussed.

## METHODS

The general methods that have been used for antimicrobial susceptibility testing of anaerobes are agar disk diffusion, agar dilution, broth macrodilution, broth microdilution, and disk elution[14] — all methods that have been developed for and used to test bacteria that grow aerobically. Although several mechanized or automated methods have been described in recent years,[15-17] they have generally been recommended for organisms growing aerobically and have not been used or recommended for testing anaerobes.

*Disk Diffusion*. This has been the bellwether method for routine testing of aerobes and facultative anaerobes, but has received little acceptance for testing anaerobic bacteria.[18] Although disk diffusion susceptibility tests specifically for anaerobes have been described, they have not been used routinely.[19,20] More recently, in a collaborative study, the method has been reevaluated for certain anaerobes and antimicrobial agents, but again problems were identified.[21]

If a disk diffusion method were to be used for anaerobes, specific breakpoints would have to be developed for use only with anaerobes. In other words, the breakpoints used for aerobic and facultative bacteria as described by the NCCLS could not be used unless it were demonstrated that these breakpoints were accurate for anaerobes. It is my recommendation, however, that the disk diffusion test not be used for testing anaerobes unless more convincing data supporting it are developed.

*Agar Dilution*. This method is recognized as an accurate method for performing antimicrobial susceptibility tests.[22] In the method, a concentration of antimicrobial agent is added to cooled, molten agar and poured into Petri plates; each plate will contain one concentration of drug onto which multiple (usually 30 to 36) strains can be inoculated. Thus, if eight concentrations of 10 drugs were to be tested, 80 test plates plus the necessary control plates would be required, whether one tested 1 strain or 36 strains. Therefore, the method is expensive, laborious, and more difficult to automate or mechanize than tests in liquid media. As a consequence, agar dilution methods have gained little acceptance in clinical laboratories for testing either aerobic or anaerobic bacteria. The method is most useful in doing batch tests, ie, organisms are saved and tested in large batches.

Nevertheless, as indicated earlier, the NCCLS standard method for susceptibility testing of anaerobes is an agar dilution method. Even so, it is seldom used routinely, but it is necessary that it be the method to which alternative methods are compared. The method is described in both the NCCLS anaerobe standard[10] and in the standard for doing MICs for organisms that grow aerobically.[22]

Although the agar dilution method is acceptable for testing for anaerobes, it is unlikely that it will ever be used routinely in most clinical microbiology laboratories.

*Broth Macrodilution.* This is the classic dilution method for performing MICs, as it was probably the first specific method for susceptibility testing described in the literature.[9] During the succeeding years, this method — often described as the tube dilution method — was performed in only a few laboratories (usually in teaching hospitals). As this method is usually performed, the antimicrobial agent is added to 1 to 5 mL of broth (hence the term macrodilution) and then serially diluted to give a series of twofold dilutions (although twofold dilutions are not necessary). Like agar dilution, this method is also expensive and laborious, and it is for these reasons that it has not been accepted as a routine method in clinical laboratories.

Some investigators believe that the macrodilution procedure is more accurate than the broth microdilution procedure because of the volume of broth used and the size of the inoculum. In our and others' experience, however, the two methods have usually yielded essentially comparable results, usually being within one dilution of each other. But even if the assertion of greater accuracy for the macrodilution method were accepted, it is unlikely that it would ever be adopted for routine use in clinical microbiology laboratories because of its inconvenience and cost.

*Broth Microdilution.* The broth microdilution method for performing MIC tests is a miniaturized version of the macrodilution method in that the tests are performed in 0.05 or 0.1 mL of broth per tube (or well) in contrast to the 1 to 5 mL used in the macrodilution test. This change in volume permits the test to be done less expensively and makes it easier to manipulate, but these changes alone do not account for the wide acceptance of this method. The major reason for the acceptance in clinical microbiology is that this method can be automated or mechanized and has been made available commercially. In the first use of this method to determine MICs, the "microtiter" method of Takatsy[23] that had been used in serologic tests was adapted in MIC testing, ie, these tests were performed in small volumes in plastic trays containing a series of wells, and serial twofold dilutions were made by hand by using the Takatsy diluters. In succeeding years equipment was developed to semiautomatically load these trays with broth containing prediluted antimicrobials.[15-17,24] Each tray would contain several different concentrations of several drugs, permitting one organism to be tested against several antimicrobials by using only one tray. This mechanization or semiautomation made it possible to prepare these trays commercially.[15-17,24] The commercial trays are either frozen or lyophilized for presentation to the customer, but each of these methods has some drawbacks. The trays with frozen broth must be kept frozen until just prior to use and thus require freezer space, whereas the trays with lyophilized drugs can be stored at room temperature, thus eliminating the need for freezer space. However, the lyophilized antimicrobials must be rehydrated prior to inoculation, thus necessitating the development of dehydration and inoculation equipment. In both the frozen and lyophilized systems, inoculators have been developed so that all wells in a tray can be inoculated simultaneously. The result of the development of these methods is that the vast majority of clinical microbiology laboratories in the United States perform MICs, and most of them are done by microdilution (most by commercial microdilution systems).[25]

For those microbiologists who perform MIC tests on anaerobes, most probably use the microdilution method.[25] Commercial microdilution systems for anaerobes are available, and some laboratories make their own trays. The reason for the more widespread use of the microdilution systems for testing anaerobes is that the method is much more convenient to use than either the agar dilution test or the broth macrodilution test, and it is available commercially.

*Disk Elution.* In this method, the source of the antimicrobial agent is a paper disk, which is placed into the appropriate volume of broth in which the drug is eluted to yield the desired concentration. In the method as it is generally used and as it is described in NCCLS document M17-P,[12] one selected concentration of each of the drugs to be tested is achieved in this manner, thereby creating a test procedure in which susceptibility and resistance are judged by whether or not an organism is inhibited by one selected concentration of antimicrobial. This method is a modification of the method described by Schneierson and Amsterdam in the 1950s,[26] and is essentially the same as the method described for the Autobac System in the 1970s.[27] The use of this method for testing anaerobic bacteria, however, was first described by Wilkins and Thiel.[28] In their method they stressed the use of the commercially available disks recommended for use in the standard disk diffusion method for bacteria that grow in air, thus making it a method that could be used in any laboratory. They used supplemented brain-heart infusion broth, inoculation under anaerobic conditions, and incubation in an anaerobic atmosphere. Results were reported as susceptible or resistant depending upon whether growth was less than 50% of the growth in the control tube (without antimicrobial agent).

This method has been done with several different broths: brain-heart infusion, Wilkins-West, Schaedler's, and thioglycollate.[12] Kurzynski et al[29] described a modification of the Wilkins-Thiel test in which they used thioglycollate broth; this modification was the one adopted by the NCCLS.[12] In the opinion of members of the subcommittee, the Kurzynski method was the easiest for most laboratorians to perform, and would be most suitable for those laboratories in which susceptibility tests on anaerobes are infrequently performed. The method is usually done with 5-mL volumes of thioglycollate, and the broth is boiled in the tubes before use to remove any dissolved oxygen. Disks that are commercially available for use in the disk diffusion method for bacteria that grow aerobically are used as elution disks to yield the desired concentration of each antimicrobial. For example, if one metronidazole disk is added to 5 mL of broth, the resulting metronidazole concentration after elution will be 16 μg/mL of broth, since the disk contained 80 μg of the drug, but to get 4 μg/mL of clindamycin would require adding 10 clindamycin disks, since each one contains 2 μg of the drug. In order to avoid having to use so many disks (and possible loss of anaerobiosis), a 10-μg clindamycin disk is being evaluated that would reduce the requirement to two disks. Each antimicrobial-containing broth and a control broth with no antimicrobial is inoculated with 0.1 mL of an actively growing culture; each tube is inverted to mix and incubated for 24 or 48 hours depending upon rate of growth. The original end point for susceptibility was no growth or less than 50% of that in the control, but present recommendations are to use growth or no growth. The results report susceptibility or resistance.

Meaningful quality control of a procedure such as this, ie, only one concentration of drug, is very difficult. However, the quality of the disks can be monitored by using standard reference strains and the diffusion methods described for organisms that grow aerobically.[30]

The elution method has received wide acceptance in clinical microbiology laboratories because of the ease with which it can be done; the majority of laboratories in the College of American Pathologists surveys reported it to be the method they used.[25] The method has not proven to be as accurate as it was originally thought, however, because more recent studies have shown that results obtained with certain antimicrobials were not accurate when compared to MICs obtained with the standard reference method.[31]

*Other Methods.* Two other methods somewhat similar to the elution method have been described for susceptibility testing of anaerobic bacteria, but have not gained much acceptance because they are not as convenient to perform as the microdilution disk and elution methods.

One of these is the category method, which is similar to the disk elution method except that three concentrations of each drug are usually tested.[14,32] This method is generally based upon an international collaborative study method,[33] and the concentrations that are chosen are based on clinical considerations or on definitions of breakpoints of susceptibility, moderate susceptibility, and resistance.[14,22] If these tests are to be done as disk elution methods, the disks of appropriate concentration will not be commercially available and will have to be made in the laboratory,[14] but alternatively the drugs can be added to the broth as powder, as in an MIC test, with the tubes of broth then being frozen until ready to use.[14]

A similar kind of test is the extended agar dilution test described by Hauser et al.[34] In this test, two concentrations of drug are tested so that susceptible, moderately susceptible, and resistant categories will be discriminated. If the organism is inhibited by both concentrations of drug it is considered susceptible, if it is inhibited by the high concentration but not the low concentration it is moderately susceptible, and if not inhibited by either, it is resistant. The tests are usually performed in quadrant or biplate Petri dishes. An advantage of this method is that several cultures can be replicated into each plate, as is done in the regular agar dilution test.[22]

Although both of these methods offer more information than the Kurzynski elution method, they obviously require much more effort and supplies to perform and are more expensive. It is probably for these reasons that they are seldom used in clinical microbiology laboratories.[25]

## DISCUSSION

The role that antimicrobial susceptibility testing should play in the clinical management of infections due to anaerobic bacteria has always been debated. In recent years, these questions were so often submitted to the NCCLS that a working group was appointed to consider them. Their conclusions and recommendations have been published[13] and are included in the second edition of the M11 standard.[11]

The Working Group considered these questions. 1) Are there situations in which susceptibility tests on anaerobes can be useful and justifiable? 2) Can these tests predict clinical and microbiologic cures? 3) Considering accuracy, predictive value, and practicality, is there a hierarchy of test methods that should be used?

In publishing their conclusions and recommendations, the group addressed four areas. 1) What are the indications for susceptibility testing? 2) What is the reliability of present in vitro susceptibility tests for anaerobes? 3) Is there a clinical role for β-lactamase testing of anaerobes? 4) Can clinical and microbiologic cures be correlated with results of susceptibility testing?

*Indications for Susceptibility Testing of Anaerobes.* The Working Group concluded that susceptibility testing of anaerobes should be done in the following situations: 1) to determine patterns of susceptibility to new antimicrobial agents, 2) to periodically monitor susceptibility patterns in various cities and countries, 3) to periodically monitor susceptibility patterns in local institutions, and 4) to assist in the management of individual patients. Cases in which tests might be done are those in which there is a failure of empiric therapy, those in which the selection of an antimicrobial agent may be pivotal to success, or those in which there is a lack of information on which to formulate empiric therapy. Examples of specific infections for which tests might be done are brain abscess, endocarditis, osteomyelitis, joint infections, infection of prosthetic devices or vascular grafts, and recurrent or refractory bacteremia. Organisms that may merit testing are the *Bacteroides fragilis* group, other *Bacteroides* spp, certain fusobacteria, *Clostridium perfringens*, and *Clostridium ramosum*. Drugs that may be considered for testing are penicillin G, certain wide-spectrum penicillins, cefoxitin, and clindamycin, as well as some newer cephalosporins active against anaerobes. Drugs to which most anaerobes are univerally susceptible — metronidazole, chloramphenicol, imipenem, and β-lactam–β-lactamase inhibitor combinations — need not be tested.

*Reliability of Present In Vitro Tests.* As indicated above, there are a number of methods for antimicrobial susceptibility testing of anaerobes, but there is no agreement as to a "gold standard." There are problems with reproducibility and/or inability to grow all significant anaerobes with essentially all methods, and there is also a lack of comparability between methods. Most of the problems with lack of comparability between methods occur with various β-lactams when tested by broth dilution and by agar dilution. Since most broth dilution tests are done by microdilution, the discrepancies are mostly between broth microdilution and agar dilution. The trend with the results for these two methods is for the MICs obtained with microdilution to be lower than those obtained with agar dilution. In some cases the differences may be great enough that one test indicates susceptibility and the other resistance for the same drug. Another factor contributing to these problems is lack of agreement on appropriate breakpoints. The breakpoints used for aerobic bacteria have been the ones used for anaerobes, but data have not been developed to show they are correct. In certain "drug-bug" combinations, the MICs may cluster at the breakpoint and cause problems of reproducibility as well as inaccurate results. If acceptable standards are achieved, performance test strains should be made available to all laboratories. The NCCLS has withdrawn the recommendation for the disk elution method because of test unreliability.[11]

*Role of β-Lactamase Testing.* Since resistance to β-lactams does not always correlate with β-lactamase production, the β-lactamase result does not necessarily correlate with resistance or clinical response. However, a positive β-lactamase test can provide some rapid, clinically relevant information in that it can predict resistance to penicillins and first-generation cephalosporins.[11] The β-lactamase test with anaerobes should be performed with a chromogenic cephalosporin, and Nitrocefin is the one most readily available.

*Clinical Correlation With Susceptibility Testing.* It has been generally recognized that correlation of the clinical outcome with the susceptibility result could be done if enough patients were studied with each drug. In most cases, these data are not available for newer drugs or for older drugs for which resistance rates are changing. Nevertheless, there are studies to show that agents with good in vitro activity against anaerobes are more likely to produce favorable results.[13] It will, however, be more difficult to correlate the susceptibility result with outcome in an individual patient. The difficulties may be with the method that was used to test the susceptibility, with characteristics of the patient that influence the clinical outcome (age, nutritional status, underlying illnesses, etc), or with the properties of the drug that was used, eg, its pharmacokinetic properties and susceptibility to enzymes produced by the bacteria or the patient. Another factor that makes correlation of susceptibility result to clinical outcome difficult is that patients may show a therapeutic response without chemotherapy or even with inappropriate surgical procedures, and with surgery or without it. The role of appropriate surgical procedures cannot be overestimated in achieving a positive response to therapy. Whenever such correlation studies of susceptibility results and clinical responses are done, they should include both clinical cures and microbiologic cures. In considering the usefulness of the in vitro susceptibility tests for anaerobes, there are also other factors that should also be considered. Adequate numbers of strains should be tested, and the species selected should reflect the frequency with which they are isolated from clinical specimens.[13] The isolates studied should include recent clinical isolates in order to ensure that emerging resistance will be recognized.

The conclusions of the NCCLS Working Group were essentially that susceptibility testing of individual patient isolates will not be required very often, because it is difficult to develop reliable predictive values and because there are several antimicrobial agents with universal activity against anaerobes. On the other hand, the methods presently used for susceptibility testing of anaerobes are useful for doing comparative studies of drugs and for monitoring development of resistance, and they should be used until better methods are developed. Furthermore, the best method would be one that is simple, quick, inexpensive, reproducible, and commercially available, uses media that supports the growth of all clinically important anaerobes, and has been shown to have a good predictive value for clinical and microbiologic cures.

Even though I concur with the majority of the conclusions and recommendations of the NCCLS Working Group and subcommittee (I am a member), it is my opinion that they will have little influence on the present patterns of testing anaerobes in clinical microbiology laboratories. I believe that clinicians will still want susceptibility data and that clinical microbiologists will provide them. It is very likely that these susceptibility results will be obtained by methods that are easier to perform and are commercially available, unless it is convincingly demonstrated that these results will be harmful to the patient.

# ROLE OF ANAEROBIC BACTERIA IN UPPER RESPIRATORY TRACT INFECTIONS

ITZHAK BROOK, MD, MSC

## INTRODUCTION

Anaerobes possess an important role in upper respiratory tract infections (URTIs). They are of particular importance in the chronic form of many of these infections. Their isolation from URTIs is explained by their predominance in the normal microflora of the oral mucous membranes.[35] The number of anaerobes in saliva is 1.1 x $10^8$/mL, compared with the aerobic count of 4 x $10^7$/mL.[36] Anaerobic bacteria outnumber aerobic microorganisms 10 to 1 in the oral cavity and 1,000 to 1 in the gastrointestinal tract.[37]

Anaerobes commonly found in the nasopharynx as normal flora and as pathogens in URTIs are *Bacteroides* sp (including *Bacteroides melaninogenicus* group and *Bacteroides buccalis*), *Fusobacterium* sp, and *Peptostreptococcus* sp (Table 1[38-63]).

Anaerobic bacteria were isolated from most URTIs in studies that used proper techniques for their transportation, cultivation, and identification. These organisms have been isolated from acute[38-40] and chronic[41-51] otitis media, peritonsillar and retropharyngeal abscesses,[52,53] recurrent tonsillitis,[54-59] suppurative thyroiditis,[60] parotitis,[61] chronic sinusitis,[62] and cervical lymphadenitis[63] (Table 1).

Many of these anaerobic as well as aerobic organisms produce β-lactamase, which may interfere with the activity of penicillin and protect penicillin-susceptible organisms from this drug.[64]

In most of these infections a polymicrobial aerobic-anaerobic flora can be isolated from the infected site. The presence of mixed flora at an infected site allows for a synergistic relationship between the different organisms that facilitates their virulence[65] and allows them to benefit from a metabolic enzymatic relationship. Anaerobic bacteria possess several virulence factors. These include the presence of a capsule,[66] the ability to adhere to mucosal epithelial cells, superoxide dismutase, catalase, immunoglobulin proteases, and coagulation promotion and spreading factors (such as hyaluronidase, collagenase, and fibrinolysin).[35] This review describes the data that support the importance of anaerobic bacteria in URTIs.

## OTITIS MEDIA

The improvement in microbiologic methods increased the awareness of the important role of anaerobic bacteria in ear infections. The predominance of anaerobic organisms in the oral flora explains their involvement in otitis media. Recognition of the role of anaerobic organisms in ear infections can influence their management, since some of these organisms are resistant to various antimicrobials. The recovery of anaerobic bacteria in otitis media correlates with the use of proper and adequate techniques of collection, transportation, and inoculation of the specimens. Many of the past studies of acute, serous, and chronic otitis media did not use proper methods for the recovery of these organisms.[67] However, whenever such techniques

TABLE 1. SUMMARY OF BACTERIA ISOLATED IN UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN

| *Type of Infection* | *Aerobic and Facultative Organisms* | *Anaerobic Organisms* | *References* |
|---|---|---|---|
| Acute otitis media | *Hemophilus influenzae**<br>*Streptococcus pneumoniae*<br>*Moraxella catarrhalis** | *Peptostreptococcus* sp | 38-40 |
| Chronic otitis media and mastoiditis | *Staphylococcus aureus**<br>*Escherichia coli**<br>*Klebsiella pneumoniae**<br>*Pseudomonas aeruginosa** | *Bacteroides* sp*<br>*Fusobacterium* sp*<br>*Peptostreptococcus* sp | 41-51 |
| Peritonsillar and retropharyngeal abscess | *Streptococcus pyogenes*<br>*Staphylococcus aureus**<br>*Streptococcus pneumoniae* | *Fusobacterium* sp*<br>*Bacteroides melaninogenicus* group*<br>*Peptostreptococcus* sp | 52, 53 |
| Recurrent tonsillitis | *Streptococcus pyogenes*<br>*Hemophilus influenzae**<br>*Staphylococcus aureus** | *Bacteroides melaninogenicus* group*<br>*Bacteroides buccalis**<br>*Bacteroides buccae**<br>*Bacteroides oris**<br>*Fusobacterium* sp* | 54-59 |
| Suppurative thyroiditis | *Streptococcus pyogenes*<br>*Staphylococcus aureus** | *Bacteroides* sp*<br>*Peptostreptococcus* sp | 60 |
| Suppurative parotitis | *Staphylococcus aureus** | *Bacteroides melaninogenicus* group*<br>*Fusobacterium* sp* | 61 |
| Chronic sinusitis | *Staphylococcus aureus**<br>*Streptococcus pneumoniae*<br>*Hemophilus influenzae** | *Bacteroides fragilis* group*<br>*Bacteroides melaninogenicus* group*<br>*Peptostreptococcus* sp | 62 |
| Cervical lymphadenitis | *Streptococcus pyogenes*<br>*Staphylococcus aureus**<br>*Mycobacterium* sp | *Bacteroides* sp*<br>*Peptostreptococcus* sp | 63 |

*Organisms that have the potential of producing β-lactamase.

were employed these organisms were recovered in substantial numbers.[35,68]

*Acute Otitis Media.* Anaerobes, mainly *Peptostreptococcus* sp, were recovered from about a quarter of 186 ear aspirates of acute otitis media. These organisms were isolated in about a third of the cases mixed with aerobic and facultative bacteria.[39] Organisms were isolated in over 90% of the studied patients, a percentage larger than in the other studies, in which methods for recovery of anaerobes were not used. However, since the external ear canal was not sterilized before aspiration, the possibility of contamination of specimens by the ear canal flora exists. In a smaller study, in which strict sterilization of the ear canal was employed, anaerobes were recovered in 3 of 28 infants.[40]

Since the anaerobes isolated in acute otitis media are susceptible to the penicillins as well as the other antimicrobials commonly used to treat acute otitis media, no change in the recommended therapy is indicated. Further studies are, however, warranted to further investigate the role of anaerobes in acute otitis media.

*Otitis Media With Effusion.* In a study of otitis media with effusion that also used methods for the cultivation of anaerobes, microorganisms were isolated in 23 of 57 (41%) of the patients.[69] Anaerobes were present as the only isolate in 17% of the culture-positive specimens, and in an additional 26% they were present mixed with aerobes or facultative organisms. The predominant anaerobes were *Peptostreptococcus* sp and *B melaninogenicus* group.

The role of aerobic as well as anaerobic microorganisms in the pathogenesis of otitis media with effusion is not yet clear; however, antimicrobial agents are often administered in an attempt to eradicate the microorganisms that are generally recovered from about half of the effusions. The presence of microorganisms, many of which produce β-lactamase, in serous ear aspirates raises the question whether antibiotics effective also against these aerobic and anaerobic β-lactamase–producing bacteria (BLPB) should be used. Controlled studies may define the value of antimicrobial treatment in patients with otitis media with effusion and clarify the role of bacteria in the pathogenesis of the inflammatory process.

*Chronic Suppurative Otitis Media.* The high number of negative cultures of chronic suppurative otitis media in some studies may be attributed to the use of inappropriate methods for recovery of anaerobes.[67] In one study[48] bacteria were seen on direct smears in 80% of middle ear aspirates, while only 40% of the effusions yielded bacterial growth. Foul-smelling pus in the middle ear may be due to the presence of anaerobic bacteria.

Several studies reported the recovery of anaerobes in about half of the patients with chronic suppurative otitis media[41,42,44-47,49-51] and half of those with chronically infected cholesteatoma.[70,71] The variability in the rate of isolation of anaerobes in these studies may be attributed to differences in the studies' locations and in laboratory methods. In several of the studies, the delays in cultivation were extensive and the length of incubation was inadequate for the recovery of anaerobic bacteria. The predominant anaerobes were *Peptostreptococcus* sp, *Bacteroides* sp, and *Fusobacterium* sp. Many of these organisms produced β-lactamase and might have contributed to the failure of these patients to respond to penicillins. Anaerobic isolates were usually mixed with other anaerobic or aerobic bacteria, and the number of isolates ranged between two and four per specimen.

The importance of anaerobes in chronic suppurative otitis media is highlighted by their recovery from most of its infectious complications. Anaerobes similar to those recovered in chronic suppurative otitis media were isolated from 23 (96%) of 24 specimens obtained from patients with chronic mastoiditis.[43] Anaerobes were recovered from most of the patients with intracranial abscesses that complicated chronic suppurative otitis media.[35,68,72]

Further support for the importance of anaerobes in chronic suppurative otitis media is provided by an investigation that showed the efficacy of antibiotics that eradicate infection in 52%[51] to 89%[73] of treated patients. However, since a control group was not included in these studies, further studies are indicated to evaluate the efficacy of the medical and surgical management of this infection.

Cholesteatoma that accompanies chronic suppurative otitis media can induce the absorption of bone. Various theories attempt to explain the factors involved in the process of expansion of cholesteatoma and the collagen degradation that occurs in its vicinity.[70] The production of organic acids by anaerobic bacteria may be involved in the destructive process.[71] Since cholesteatoma associated with chronic suppurative otitis media contains bacteria similar to those recovered from chronically infected ears, the cholesteatoma may serve as a nidus of the chronic infection.[72]

## CHRONIC SINUSITIS

Anaerobes are often recovered from chronically inflamed sinuses. Although they are generally isolated from only about 10% of patients with acute sinusitis, they can be recovered from up to two thirds of patients with chronic infections.[35,68] The reduction in the oxygen tension and the increase in the bicarbonate contents in the sinuses takes place as the inflammation persists, and facilitates the growth of anaerobes as the infection becomes chronic. The predominant anaerobes recovered are *Peptostreptococcus* sp and *Bacteroides* sp.[35,68] An average of almost three anaerobes per sinus aspirate was recovered in children with chronic sinusitis.[62]

Infection of the sinus, when not treated promptly and properly, may spread via anastomosing veins or directly to nearby structures, including the central nervous system. The first warning sign of extension of the infection may be the appearance of orbital cellulitis.[74] Intracranial complications include retrograde meningitis, cavernous sinus thrombosis, and epidural, subdural, and brain abscesses.[72] The response of patients to antimicrobial therapy is often inadequate and unpredictable, even when appropriately administered.[74] This may be because of the poor penetration of the antimicrobial to the infected sinus space, and its inactivation by the pus. Surgical drainage is of paramount importance, especially if no clinical improvement has occurred, and should not be delayed for more than 48 hours after antimicrobial therapy has been initiated. In many cases it should be an integral part of management.

## PHARYNGOTONSILLITIS

Group A β-hemolytic streptococci (GABHS), *Staphylococcus aureus*, *Streptococcus pneumoniae*, and viruses are generally associated with tonsillar and peritonsillar infections. However, anaerobes also have been isolated from the cores of tonsils of children with recurrent GABHS[54] and non-GABHS[58] peritonsillar[52] and retropharyngeal[53] abscesses. β-Lactamase–producing strains of *Bacteroides* sp, *Fusobacterium* sp, and *S aureus* were isolated from the tonsils of 74% of children with GABHS recurrent tonsillitis[54-57] and from 40% of children with non-GABHS tonsillitis.[58] Similar organisms were recovered from patients with adenoiditis and adenoid hypertrophy.[75]

The possible role of anaerobes in the acute inflammatory process in the tonsils is supported by several clinical observations: the recovery of anaerobes in abscesses of the peritonsillar or the retropharyngeal area, in many cases without any aerobic bacteria,[52,53] their isolation in well-established anaerobic infections of the tonsils (Vincent's angina),[35] the increased recovery rate of encapsulated *B melaninogenicus* group in acutely inflamed tonsils,[76] their isolation from the cores of recurrently inflamed non-GABHS tonsils,[58] and the response to antibiotics in patients with non-GABHS tonsillitis.[77-81]

Several studies in which metronidazole was given to patients with infectious mononucleosis support the role of anaerobes in tonsillitis.[77,78] Metronidazole therapy alleviated the symptoms of tonsillar hypertrophy and shortened the duration of fever. Metronidazole has no efficacy against viruses or aerobic bacteria and is only effective against anaerobes.[35] A possible explanation of its action could be suppression of the oral anaerobic flora, which might have contributed to the inflammatory process induced by the Epstein-Barr virus.[77,78]

McDonald et al[79] reduced the severity of symptoms of adults with non-GABHS tonsillitis by the administration of erythromycin. Merenstein and Rogers[80] observed an improvement in the symptoms of patients with acute non-GABHS tonsillitis following penicillin therapy, as compared to placebo. Putto[81] demonstrated an earlier defervescence following penicillin therapy of children with non-GABHS tonsillitis as compared to patients with viral tonsillitis. All of these studies suggest that bacteria other than GABHS, including anaerobes, may be involved in acute tonsillitis. However, since no proof of that hypothesis is yet available, these observations have no practical implications at the present, and await further studies.

Recurrent pharyngotonsillitis due to GABHS is still a serious clinical problem. Failure to eradicate the streptococci from patients treated with penicillin can occasionally lead to rheumatic fever and, rarely, to glomerulonephritis. As a last resort many physicians refer their patients for elective tonsillectomy.

One explanation for this penicillin failure is that repeated penicillin administrations result in a shift in the oral microbial flora with selection of BLPB, eg, strains of *Hemophilus* sp, *S aureus, Moraxella catarrhalis*, and *Bacteroides* sp,[64] that by degrading penicillin in the area of the infection can protect not only themselves but also penicillin-susceptible pathogens. The recovery of aerobic and anaerobic BLPB in over three fourths of the patients with recurrent GABHS tonsillitis,[54-57] the ability to measure β-lactamase activity in the core of their tonsils,[82] and their response to antimicrobials effective against BLPB (ie, clindamycin or amoxicillin plus clavulanic acid)[59,64,83] support the role of these organisms in the inability of penicillin to eradicate GABHS tonsillitis.

## CONCLUSION

Infections of the upper respiratory tract often involve mixed aerobic and anaerobic organisms. Anaerobes contribute to the severity and chronicity of infections that occur in the sinuses, the nose, and various other sites in and around the oral cavity.[68] These organisms were recovered in cases of chronic otitis media,[39,40,65-69] cholesteatoma,[70,71] chronic mastoiditis,[43] chronic sinusitis,[62] adenoiditis,[75] recurrent tonsillitis,[54-57] peritonsillar abscess,[52] and retropharyngeal abscess.[53] The anaerobes include organisms such as *B melaninogenicus* and *Bacteroides oralis, Fusobacterium*, anaerobic cocci, and *Actinomyces*. When making choices for therapeutic management of these infections, one should use antimicrobial agents effective against these organisms, recognizing, of course, that these entities require not only antimicrobial therapy but primary surgical intervention.

# ANAEROBES IN OTITIS MEDIA AND SINUSITIS

ELLEN R. WALD, MD

## OTITIS MEDIA

The precise role of anaerobic isolates as a cause of otitis media has been controversial. Potential problems regarding the recovery and interpretation of anaerobic isolates result from failure to observe strict antisepsis of the external auditory canal, aeration during collection of and delay in plating specimens, failure to maintain anaerobic conditions during transport, inadequate media for isolation of anaerobes, improper conditions for the growth of anaerobes, and abbreviated incubation time. To review the prevalence of anaerobes in otitis media, it is best to divide middle ear infections into acute and chronic forms.

In most studies of acute otitis media in which tympanocentesis has been performed after proper cleansing of the external auditory canal, aerobic isolates predominate. The usual bacterial species in their relative order of prevalence are shown in Table 2.[84] *Streptococcus pneumoniae, Hemophilus influenzae,* and *Moraxella catarrhalis* are most common; *Streptococcus pyogenes* and staphylococcal species account for a few percent of the isolates. The large proportion of sterile middle ear fluids in every series of patients with acute otitis media prompts the consideration of anaerobes as potential pathogens.

Nonetheless, few or no anaerobes have been recovered in most series of patients with acute otitis media. In a very small study by Brook and Schwartz[40] (in which there was proper attention to preparation of the external auditory canal prior to tympanocentesis) 28 patients with acute otitis media underwent tympanocentesis; middle ear aspirates were evaluated meticulously for aerobes and anaerobes. Anaerobes were recovered from 3 patients (10.7%); in only 1 patient was an anaerobic species the sole pathogen recovered. It can probably be safely concluded that respiratory anaerobes cause no more than 5% to 10% of cases of acute otitis media.

In the past it was assumed that the middle ear fluid in patients with chronic otitis media with effusion (behind an intact tympanic membrane) was sterile. However, in 1958 Senturia et al[85] recognized that some substantial portion of patients with otitis media with effusion do have positive bacterial cultures of their middle ear aspirates. The number of positive cultures has varied from 20% to 66%; however, anaerobes have been infrequently isolated in studies reported from Columbus, Ohio; Boston, Mass; Minneapolis, Minn; and Pittsburgh, Pa.[86-90]

Brook et al[69] recovered bacteria from 23 of 57 (40.3%) patients with at least 6 months of persistent middle ear effusion found to be serous at the time of tympanostomy tube placement. Anaerobic isolates were found in 4 patients and mixed aerobic and anaerobic bacteria in 6 patients. Accordingly, anaerobes were recovered from 17.5% of patients. There were five anaerobic gram-positive cocci, five isolates of *Bacteroides melaninogenicus,* and three isolates of *Propionibacterium acnes*. As the latter may represent skin contaminants, anaerobes are probably recovered from no more than 10% to 15% of patients with chronic middle ear effusion and an intact tympanic membrane.

The group of patients with otitis media in whom anaerobic bacteria are most readily and uniformly implicated are patients with chronic suppurative otitis media. Anaerobes have been recovered from 6% to 59% of such patients.[47,50,91-93] In a most rigorous assessment, Brook and Finegold[41] recovered anaerobic bacteria from 51% of ear aspirates obtained from children with chronic suppurative otitis media. The ear aspirates were innoculated immediately onto enriched media supportive for the growth of anaerobes and incubated for 14 days. The majority of the anaerobic isolates were anaerobic gram-positive cocci, *Bacteroides* species (including *Bacteroides fragilis* and *B melaninogenicus*), and *Fusobacterium nucleatum*. The predominant aerobic bacteria isolated were enteric gram-negative rods (mostly *Pseudomonas aeruginosa*) and *Staphylococcus aureus*. Anaerobic isolates were usually mixed with other bacteria and the number of isolates ranged between two and four per specimen.

In summary, anaerobes are isolated approximately 5% to 10% of the time in acute otitis media, 10% to 15% of the time in chronic otitis media with effusion, and at least 50% of the time in patients with chronic suppurative otitis media.

## SINUSITIS

To consider the role of anaerobes in paranasal sinusitis we must systematically review the situation for acute, subacute, and chronic forms of this illness. Establishing the bacterial cause in cases of maxillary sinusitis is technically more difficult than in cases of otitis media. The preferred method of aspirating the maxillary sinus in children is by passing a large-bore trocar (Fig 1) beneath the inferior turbinate across the lateral nasal wall. This sampling technique is deemed safer than attempting to cannulate the natural meatus, which might inadvertently traumatize the area and lead to scarring. The Caldwell-Luc approach for access to the maxillary sinus is not acceptable in children for culture sampling because of the developing dentition.

The indicated approach presents problems, because the nasal vestibule is heavily colonized with aerobic and anaerobic bacterial species that may result in contamination

TABLE 2. DISTRIBUTION OF PATHOGEN TYPE IN EFFUSIONS CULTURED

| | *Acute OME* | *Chronic OME* | *Total* |
|---|---|---|---|
| *Hemophilus influenzae* | 341 (31.3%) | 402 (35.2%) | 743 (33.3%) |
| *Streptococcus pneumoniae* | 437 (40.2%) | 234 (20.5%) | 671 (30.1%) |
| *Moraxella catarrhalis* | 199 (18.3%) | 264 (23.1%) | 463 (20.6%) |
| *Streptococcus pyogenes* | 56 ( 5.2%) | 27 ( 2.4%) | 83 ( 3.7%) |
| *Staphylococcus aureus* | 26 ( 2.4%) | 100 ( 8.8%) | 126 ( 5.7%) |
| *Pseudomonas aeruginosa* | 28 ( 2.6%) | 115 (10.1%) | 143 ( 6.4%) |
| Total | 1,087 | 1,142 | 2,229 |

Information from Krenke et al.[84]
OME — otitis media with effusion.

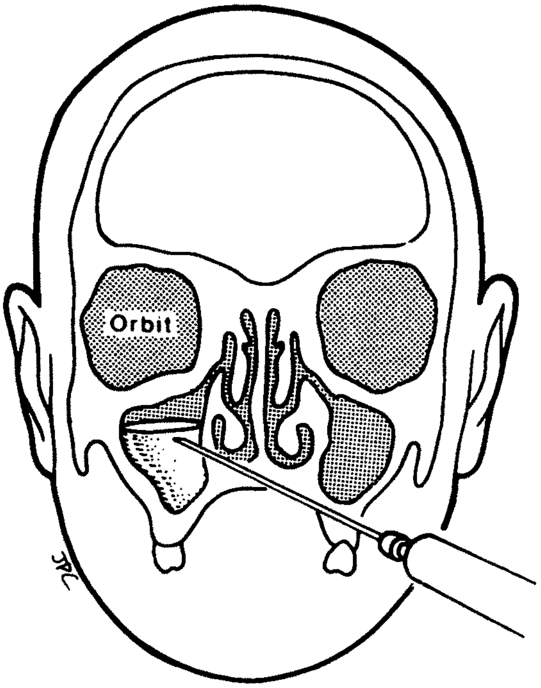


Fig 1. Aspirating maxillary sinus in children by large-bore trocar beneath inferior turbinate across lateral nasal wall. (Reprinted with permission from Bluestone CD, Stool SE, eds. Pediatric otolaryngology. Philadelphia, Pa: WB Saunders, 1983.)

of the maxillary aspirate. This possibility can be overcome or compensated for by attempting to sterilize the nasal mucosa topically, defining infection as the recovery of bacteria in high colony count (at least $10^4$ colony-forming units [CFU] per milliliter, rather than simply the recovery of any bacteria) and correlating the interpretation of the Gram stain of maxillary sinus secretions with results of bacterial cultures. It might be expected, for example, that bacteria in low colony count (contaminating bacteria) would not be seen on Gram stain. Accordingly, a positive culture and negative Gram stain might suggest contamination.

Maxillary sinus secretions are often too thick to be easily aspirated. Accordingly, irrigation of maxillary sinus secretions is required in about 50% of patients. Irrigation complicates the quantitation of bacteria and results in aeration of the specimen that may impair the recovery of anaerobes. Again, the Gram strain interpretation is helpful. Inadequate methods or a spoiled culture should be suspected when the Gram stain is positive and the cultures are negative.

Relatively few studies of acute sinusitis have been performed in the United States over the past 10 years. However, using identical techniques for adult and pediatric patients, researchers at the University of Virginia and the University of Pittsburgh have identified the bacterial flora of acute maxillary sinusitis.[94,95] Investigators at both centers have attempted to avoid nasal contamination, employed appropriate techniques for the recovery of aerobes and anaerobes, and quantitated bacterial cultures. A culture is considered positive only if a bacterial species is recovered in a colony count of at least $10^4$ CFU/mL. The prominent bacterial agents have been shown to be *S pneumoniae* and *H influenzae* in both age groups, added to by *M catarrhalis* in pediatric patients. Anaerobic isolates accounted for 9% of the positive cultures among 86 positive aspirates obtained from adults.[96] Only a single anaerobe, a peptococcus, was recovered in high colony count when 50 children with acute sinusitis underwent sinus aspiration.[97] In these studies, Gram stains and culture results were highly correlated, thereby suggesting that the isolation of anaerobes in low frequency was an accurate reflection of their relative prevalence. In contrast to these results, European investigators have reported anaerobes in 23% to 33% of cases of acute maxillary sinusitis in adults.[98-100] Purulent drainage was more likely than serous secretions to yield anaerobes. However, aspiration in these studies was usually conducted by the transnasal route without attempts to sterilize the nasal mucosa or quantitate organisms. Consequently, these studies may overrepresent anaerobes.

We recently compiled data on the bacterial flora of sinus aspirates in 40 children with subacute sinusitis.[101] These children had been symptomatic with nasal discharge or cough or both for 30 to 120 days. All were ambulatory patients (without underlying conditions) evaluated as part of several different antimicrobial trials. *Streptococcus pneumoniae, H influenzae*, and *M catarrhalis* were the common bacterial isolates. Anaerobic organisms were not isolated in high colony count from any of the children. In two patients, two anaerobic species each were isolated in colony counts of 100 or less.

Another evaluation of patients with subacute maxillary sinusitis was undertaken in patients with cystic fibrosis.[102] The most common aerobes recovered were *P aeruginosa*, nontypeable *H influenzae*, and α-hemolytic streptococci. Anaerobic bacterial species were recovered from 5 of 34 (15%) sinus aspirates in high colony count. Once again there was an excellent correlation of Gram stain interpretation and results of cultures.

In general, there has been no dispute about the importance of anaerobes in chronic sinusitis. Brook studied 40 children with symptoms of sinusitis for more than 30 days, identified as patients with chronic sinusitis.[62] He recovered anaerobes in 92% of patients, often as part of a polymicrobial process. The common anaerobes recovered were anaerobic gram-positive cocci, *Bacteroides* species, and *Fusobacterium* species. These children were almost certainly more severely ill and sick longer than our population of children with subacute sinusitis. Some of his subjects had underlying conditions predisposing them to sinusitis (such as asthma, cystic fibrosis, or local intranasal problems) and others had their cultures performed at the time of frontal trephination or ethmoidectomy — procedures unlikely to be undertaken unless the patient had significant morbidity.

Frederick and Braude[103] found anaerobic bacterial species in more than half (52%) of 83 specimens collected intraoperatively during the performance of frontoethmoidotomy or radical antrotomy via the canine fossa. The interpretation of these data is simplified because nasal contamination was avoided. However, most of their patients had very long-standing disease (10 years) and the procedures were performed for clinical indications. The applicability of these results to the individual with a shorter duration of illness and less severe symptoms is not known. Other studies of adult patients with chronic sinusitis, while uniformly testifying to the importance of anaerobes, are flawed by the same problems alluded to previously — failure to sterilize the nasal mucosa and to quantify bacteria — thereby potentially overestimating the role of anaerobes.

In summary, anaerobes seem to be a relatively infrequent cause of acute and subacute sinusitis in children and adults. However, anaerobes are recovered from the majority of patients with long-standing symptoms of sinusitis, particularly those in whom chronic morbidity has led to surgical intervention.

# ROLE OF ANAEROBIC BACTERIA IN SINUSITIS AND ITS COMPLICATIONS

ANN SULLIVAN BAKER, MD

## INTRODUCTION

The complications of sinusitis and otitis are often life-threatening owing to the proximity of the intracranial structures. The progression may be slow because of the combination of anaerobic and aerobic organisms and difficult to recognize because of the complex facial and neuroanatomy. The three major complications of acute and chronic sinusitis include spread of infection to contiguous bone, intracranial extension, and ocular involvement. We will review the bacteriology of acute and chronic sinusitis and then define the complications of sinusitis.

## SINUSITIS IN GENERAL

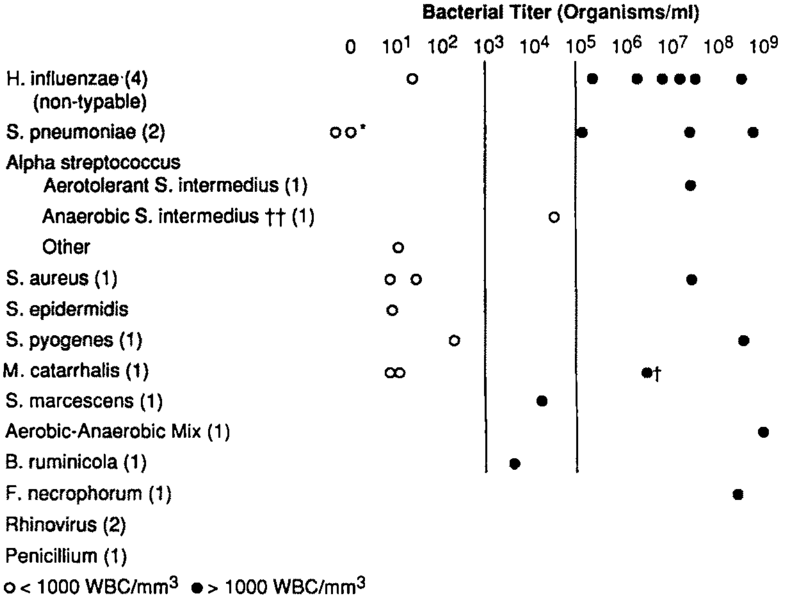
The bacteriology of sinusitis has been poorly defined owing to technical difficulties in obtaining cultures. Evans et al[94] and Hamory et al[104] found that the most common pathogens in adult acute maxillary sinusitis are pneumococci, *Hemophilus influenzae*, and anaerobic and gram-negative bacteria (Fig 2[94]). Whether the same mix of organisms plays a role in frontal and ethmoid sinusitis needs to be determined. Wald et al[95] found similar organisms in inflamed maxillary sinuses in children, with the addition of *Moraxella catarrhalis* in children less than 5 years old. There is a poor correlation between nasopharyngeal cultures and bacteria isolated from sinus aspirates, unless one constricts the mucosa and aspirates directly from the ostium.

Chronic sinusitis may follow repeated episodes of acute infection, with thickening of the sinus mucosa and continual partial obstruction. The patient with chronic sinusitis may complain of a steady headache, localized tenderness, and intermittent purulent nasal discharge. The sinus radiographs in these patients demonstrate opacification of the sinus and sclerosis of the bony sinus margins. In some patients, chronic frontal or supraorbital ethmoid sinusitis takes the form of a mucocele, a slowly expanding cyst filled with mucinous secretions, that may erode the walls of the sinus. No active signs of inflammation accompany a mucocele, unless it becomes secondarily infected to form a pyocele. In the patient with recurrent sinusitis, one should consider underlying conditions such as immotile cilia syndrome and granulomatous diseases such as Wegener's granulomatosis.

The bacteriology of chronic sinusitis was carefully evaluated by Frederick and Braude[103] from surgical specimens of frontal and ethmoid sinuses (Table 3). As expected, cultures were mixed; *Staphylococcus aureus*, streptococci, and anaerobes were obtained from one third of these specimens. Karma et al[105] and Brook[62] confirmed these studies.

*Sphenoid Sinusitis in Particular.* Sphenoid sinus infection is often unrecognized or misdiagnosed in initial evaluation. This sinus is deep in the apex of the nasal cavity, is not accessible to direct clinical examination, and may not be clearly seen on routine anteroposterior sinus films. Because of its proximity to the cavernous sinus, cranial nerves III, IV, V, and VI, and meninges, spread of infection of this cavity may result in serious complications (Fig 3[106]). Lew et al[106] studied 30 cases of sphenoid infection at Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital.

*Staphylococcus aureus* and streptococci were the most common organisms found at operation in acute and chron-



* Isolated from mouse only

† The titer of this culture was $10^3$/ml but quantitative gram stain revealed $10^6$/ml

†† *Streptococcus intermedius* is a species of alpha streptococcus which varies in aerotolerance. Strict anaerobic strains were previously designated *Peptostreptococcus intermedius*.

Fig 2. Maxillary antrum cultures in 24 adults with acute sinusitis (65 needle punctures). (Reprinted with permission.[94])

TABLE 3. BACTERIA ISOLATED AT OPERATION IN CASES OF CHRONIC SINUSITIS

| *Organism* | *No. of Specimens* |
|---|---|
| Aerobic | |
| *Staphylococcus aureus* | 14 |
| *Streptococcus viridans* | 12 |
| *Hemophilus influenzae* | 8 |
| *Neisseria subflava* | 7 |
| *Staphylococcus epidermidis* | 6 |
| Pneumococcus | 4 |
| *Escherichia coli* | 3 |
| *Moraxella catarrhalis* | 3 |
| *Hemophilus hemolyticus* | 2 |
| *Alcaligenes faecalis, Pseudomonas aeruginosa, Streptococcus pyogenes, Corynebacterium, Sarcina* | 1 each |
| Anaerobic | |
| Anaerobic streptococci | 28 |
| *Corynebacterium* | 19 |
| *Bacteroides* species | 19 |
| *Veillonella* | 14 |

All organisms recovered are listed regardless of amount of growth. Modified from Frederick and Braude.[103]

ic sphenoid sinusitis; gram-negative organisms were also found in surgical specimens of chronic sinusitis. Anaerobic streptococci were found in four cases in this retrospective study. The diagnosis of sphenoid sinusitis is best made by computed tomography (CT) scan.

Since the diagnosis was often missed on admission, appropriate therapy was frequently delayed. Seven patients with acute disease received high-dose intravenous antibiotics; these 7 recovered without sequelae. All 8 sphenoid sinusitis patients whose therapy was delayed developed serious complications or died. Major complications occurred in 50% of the acute cases, including 5 cases of cavernous sinus thrombosis and 6 cases of bacterial meningitis. Eight of the 11 acute patients required surgical drainage for cure. At operation, the sphenoid sinuses were found to be filled with pus, often under pressure (empyema). Twelve of 15 patients with chronic disease failed with antibiotic therapy alone and required surgical drainage of the sphenoid sinus, but the chronic group had fewer complications.

The patient who presents with a severe possible sphenoid sinusitis headache needs sinus CT in addition to routine lateral sinus films. If the sinus is opacified and the patient has an elevated white blood cell count and/or meningeal signs, hospital admission should be considered. If cranial nerve deficits are noted, cranial CT scan with contrast dye should be obtained. The sphenoid sinus should be cannulated to obtain specimens for Gram stain and culture and to partially relieve any empyema. Parenteral antibiotics should be started, based on the Gram stain. Nafcillin and chloramphenicol or a third-generation cephalosporin would be the antibiotics of choice. If on antibiotic treatment symptoms persist more than 2 days, or neurologic signs develop, the sphenoid sinus should be drained surgically by a wide sphenoidostomy.

COMPLICATIONS OF SINUSITIS

Three major complications of sinusitis include contiguous spread to the bone, intracranial extension, and ocular involvement.

*Frontal Osteomyelitis.* Infection of the frontal sinus mucosal wall may spread to the bone directly or by thrombophlebitis of the veins from the sinus mucosa to the diploic veins of the frontal bone. The diploic veins cross suture lines, and frontal osteomyelitis may present in areas distant from the frontal sinus (Fig 4[107]). The spread is often external to the outer table, and if so, may result in cortical breakthrough and a subperiosteal abscess (Pott's puffy tumor).[108-112] Inferior extension results in involvement of the upper ethmoid cells, the roof of the orbit, and a subperiosteal abscess. Posterior extension results in an epidural abscess. Clinically, the patient with an anterior subperiosteal tumor or Pott's puffy tumor presents with a tender soft swelling in the frontal area.

The bacteriology of frontal osteomyelitis is similar to that of chronic sinusitis, ie, anaerobic streptococci, staphylococci, and/or a mixture of organisms according to Baker (unpublished observations, 1989) and Bluestone and Steiner.[107]

Therapy should include 4 weeks of intravenous therapy

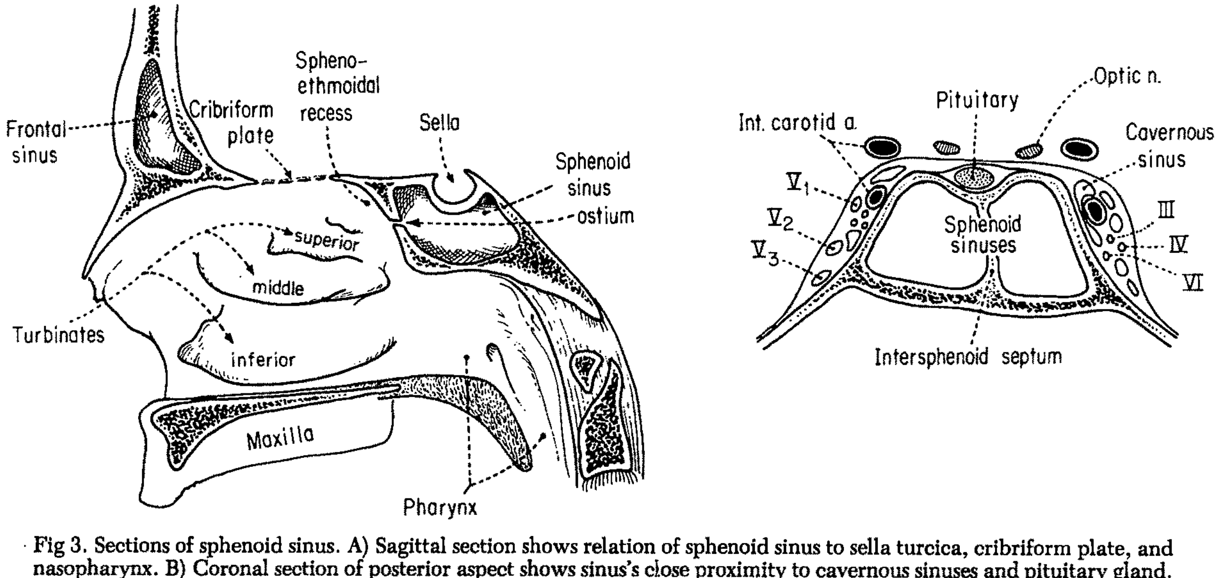


Fig 3. Sections of sphenoid sinus. A) Sagittal section shows relation of sphenoid sinus to sella turcica, cribriform plate, and nasopharynx. B) Coronal section of posterior aspect shows sinus's close proximity to cavernous sinuses and pituitary gland. (Reprinted with permission.[106])

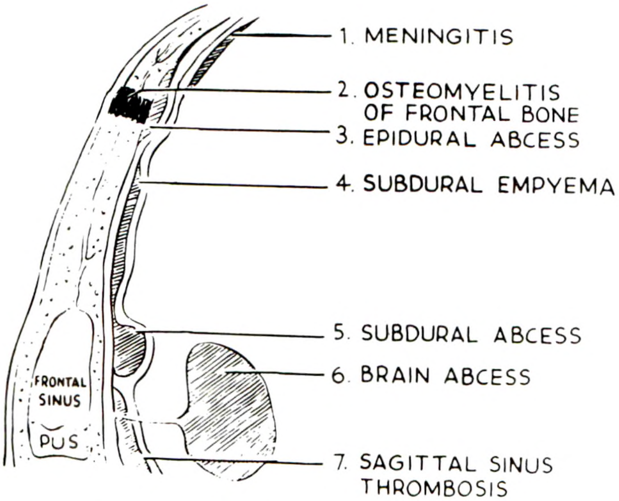


Fig 4. Intracranial complications of acute frontal sinusitis. Three major localized intracranial suppurative lesions include cerebral epidural abscess, subdural empyema, and cerebral abscess. Less common are thrombosis of large dural sinuses and cortical thrombophlebitis. (Reprinted with permission.[107])

with antibiotics such as a semisynthetic penicillin and chloramphenicol, metronidazole, or a third-generation cephalosporin for central nervous system penetration as well as anaerobic coverage. Ultimately, the frontal sinus may need to be debrided and obliterated.

*Intracranial Extension.* In addition to anterior spread from the frontal sinus, the same patient may have posterior or intracranial extension. Three major intracranial complications of sinusitis include cerebral epidural abscess, subdural empyema, and brain abscess (Fig 4).

Fever, pain, and local tenderness are the most common findings in a cerebral epidural abscess, but it is difficult to make this diagnosis. It is important to evaluate the posterior wall of the frontal sinus on CT scan; if frontal sinusitis does not respond to medical treatment, drainage may be needed.

Subdural empyema is a collection of pus in the potential space between the dura and the arachnoid.[113] More than half of the cases of subdural empyema at Massachusetts General Hospital and Massachusetts Eye and Ear Infirmary develop in patients with chronic frontal sinus infection.[114]

The symptoms and signs of the preceding infection, ie, osteomyelitis, often blend into those of subdural empyema. Swelling of the tissue over the infection may be prominent and an important clue. The headache is initially mild and limited to the area over the subdural infection. As the illness progresses, headache becomes generalized and severe. High fever, vomiting, nuchal rigidity, and finally coma develop over 2 to 3 days. Skull films may show evidence of sinusitis or mastoiditis; they are abnormal 90% of the time. The single most useful study is a CT scan with contrast; in this complication it reveals an area of low absorption exterior to the brain. The cerebrospinal fluid formula is compatible with a parameningeal focus, ie, a high protein, normal glucose, and an elevated white blood cell count.

The bacterial flora is similar to that of chronic sinusitis, ie, streptococci (one-third anaerobes) account for 70%, staphylococci account for 12%, and anaerobic gram-negative bacteria account for 8%, of which *Fusobacterium* and *Bacteroides* are the most common; the remaining 10% consisted of diphtheroids, *Hemophilus*, *Lactobacillus*, and aerobic gram-negative bacilli (from Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital surgical data and summary of the literature; Table 4[115]).

TABLE 4. RESULTS OF BACTERIAL CULTURES IN 124 PATIENTS WITH SUBDURAL EMPYEMA SECONDARY TO PARANASAL SINUSITIS

| | | |
|---|---|---|
| Streptococci (aerobic and microaerophilic) | | 54 |
| Viridans | 8 | |
| β-Hemolytic | 9 | |
| Microaerophilic | 3 | |
| Pneumococcus | 2 | |
| Not further identified | 32 | |
| Staphylococci | | 15 |
| *Staphylococcus aureus* | 10 | |
| *Staphylococcus epidermidis* | 5 | |
| Anaerobic gram-positive cocci | | 32 |
| *Peptococcus* spp | 3 | |
| *Peptostreptococcus* spp | 5 | |
| Not further identified | 24 | |
| Diphtheroids | | 4 |
| Anaerobic gram-negative bacteria | | 10 |
| *Bacteroides* spp | 4 | |
| *Fusobacterium* spp | 5 | |
| Other | 1 | |
| Aerobic gram-negative bacilli | | 3 |
| *Pseudomonas* spp | 1 | |
| *Klebsiella* spp | 1 | |
| Other | 1 | |
| *Hemophilus* spp | | 2 |
| *Lactobacillus* spp | | 1 |
| Sterile* | | 19 |

Modified from Kaufman et al,[115] who used their study and data from others. Only results of surgically obtained specimens or blood cultures are included.

*Anaerobic techniques were not always employed in processing of these cultures; in fact, authors on several occasions commented on presence of organisms on Gram-stained smears of surgical specimens.

The patient with subdural empyema needs immediate and adequate surgical drainage of the subdural abscess by multiple bur holes or a craniotomy; the sinus also requires drainage. Antibiotic therapy should cover staphylococci and anaerobic organisms.[116]

A third intracranial complication of sinusitis is thrombosis of the major dural sinuses; the cavernous, lateral, and superior sagittal sinuses are most often involved. The cavernous sinus receives venous channels from facial veins communicating with angular and ophthalmic veins and is close to the sphenoid sinus, as mentioned (Fig 3[106]). Of interest, in the cases of cavernous sinus thrombosis at the above two Boston hospitals in the past 15 years, reviewed by Southwick et al,[114] most have been secondary to sphenoid sinusitis. Other causes include facial, mastoid, and tooth infections.

The patient with cavernous sinus thrombosis complains of headache and eye pain. Findings include swelling of the forehead, lid edema, chemosis, and paralysis of the ocular muscles. It may be difficult to distinguish from orbital cellulitis; engorgement of the retinal veins and/or bilateral findings are an indication. The patient is also severely ill with headache, fever, chills, and altered consciousness.

TABLE 5. BACTERIOLOGY OF SEPTIC CAVERNOUS SINUS THROMBOSIS

| | *Boston Series (Cultures Obtained in 5 Cases)* | | *Literature (59 Cases)* | |
|---|---|---|---|---|
| *Bacterial Species* | *No.* | *%* | *No.* | *%* |
| *Staphylococcus aureus* | 2 | 40 | 42 | 71 |
| *Streptococcus* species | 1 | 20 | 10 | 17 |
| Pneumococcus | 0 | 0 | 3 | 5 |
| Gram-negative bacilli | 0 | 0 | 3 | 5 |
| *Bacteroides* species | 0 | 0 | 3 | 5 |
| *Fusobacterium* species | 1 | 20 | 0 | 0 |
| Other | 1 | 20 | 0 | 0 |

Modified from Southwick et al.[114]

The patient may be recognized as having meningitis, but not necessarily cavernous sinus thrombophlebitis secondary to sphenoid sinusitis. Predominant organisms in the literature series include *S aureus* (50% to 70%), streptococci (20%), and gram-negative anaerobes[62,114] (Table 5[114]).

Treatment of thrombosis of dural sinuses includes surgical drainage of the infected sinus or focus and high-dose intravenous therapy with a semisynthetic penicillin such as nafcillin and a third-generation cephalosporin, chloramphenicol, or metronidazole.

*Orbital Complications of Sinusitis*. Smith and Spencer[117] and Chandler et al[118] classified orbital involvement secondary to sinusitis into five stages.

The first stage is that of inflammatory edema. Swelling of the eyelids may occur as a result of sinusitis without actual orbital infection. The eyelids are not tender. There is no impairment of visual acuity or extraocular movement. Management is directed toward the primary sinus infection. This complication is most often seen in the young child with ethmoid sinusitis. This patient should be admitted for a minimum of 5 days and undergo intravenous therapy followed by a total of 2 to 4 weeks of oral therapy.

In the second stage, orbital cellulitis results from the direct spread of bacteria from the sinus, especially the ethmoid, through the orbital walls. Sinusitis accounts for 85% of cases of orbital cellulitis in the series of Trono et al.[119] Signs and symptoms include fever, rhinorrhea, headache, lid edema, orbital pain, and tenderness on palpation of the lid. Progression of infection results in dark red coloration, increased warmth of the lids, proptosis, conjunctival hyperemia, and chemosis (or swelling of the conjunctiva). There is limitation of mobility, and pain on attempted motion. Vision is normal in the early stage. Most important, there is no lateral or vertical displacement of the globe.

The bacteriologic findings of orbital cellulitis include anaerobes, streptococci, and *S aureus* (Table 6[119]). Cultures were obtained from blood cultures, transnasal aspiration of the sinuses, and intraoperative culture of the sinuses or orbital contents.

A workup should include immediate sinus films or, optimally, a CT scan. The CT scan is useful in delineating sinuses and orbital masses. The patient needs parenteral antibiotics of 2 weeks or more, humidification, and nasal spray to shrink mucosal tissue and promote drainage. If proptosis and pain progress on medical treatment, the sinus should be surgically drained by the second or third day.

TABLE 6. BACTERIOLOGIC FINDINGS IN 22 PATIENTS WITH ORBITAL CELLULITIS AND POSITIVE CULTURES

| *Organism* | *Single Isolate (13 Pts)* | *Multiple Isolates (9 Pts)* | *Total* |
|---|---|---|---|
| Aerobic bacteria | | | |
| Gram-positive organisms | | | |
| *Staphylococcus* | 7 | 1 | 8 |
| Coagulase-negative *Staphylococcus* | 1 | 2 | 3 |
| β-Hemolytic streptococci | 0 | 2 | 2 |
| Viridans streptococci | 1 | 5 | 6 |
| Nonhemolytic streptococci (not *Enterococcus*) | 0 | 2 | 2 |
| *Streptococcus pneumoniae* | 2 | 0 | 2 |
| Other (*Lactobacillus*, *Corynebacterium hemolyticum*) | 0 | 2 | 2 |
| Gram-negative organisms | | | |
| *Hemophilus influenzae* | 0 | 2 | 2 |
| Other (*Hemophilus parainfluenzae*, *Escherichia coli*, *Neisseria* spp) | 0 | 1 | 1 |
| Anaerobic bacteria | | | |
| Mouth flora anaerobes | | | |
| (*Fusobacterium* spp, *Bacteroides* spp, streptococci, etc) | 2 | 7 | 9 |
| *Clostridium perfringens* | 0 | 1 | 1 |

Modified from Trono et al.[119]

In the third stage, a subperiosteal abscess results from direct extension from within the sinus, especially ethmoid or frontal. Pus collects between the periorbita and the bony wall of the orbit. The most helpful clinical clue is displacement of the globe; since the primary sites of concern are ethmoidal and frontal sinuses, displacement tends to be downward or lateral. There may or may not be chemosis. This patient needs rapid evaluation with drainage by a combined otolaryngology-ophthalmology team.

The fourth stage, an orbital abscess, results from consolidation of infection in orbital cellulitis or rupture of pus from the periorbit. Progression of infection in the patient with orbital cellulitis despite adequate intravenous antibiotics, decreased visual acuity, or extraocular movement suggests the development of an intraorbital abscess. Again, the globe is usually displaced downward and laterally. There is complete ophthalmoplegia and a severe decrease in vision.

Finally, cavernous sinus thrombosis may be a late complication of orbital cellulitis. Diagnosis can be confirmed by CT scan with contrast[120] or by magnetic resonance imaging.

In summary, in the patient with orbital cellulitis, one should consider sinus infection. If the patient does not improve in 24 hours with medical therapy, consider surgical intervention with the help of the otolaryngology and ophthalmology services. Subperiosteal and orbital abscesses usually require drainage by a combined otolaryngology-ophthalmology team.

## COMPLICATIONS OF OTITIS

*Local Complications of Acute Otitis Media*. The local complications of acute otitis media include hearing loss, recurrent otitis media, and acute mastoiditis.[121] Symptoms

TABLE 7. BACTERIOLOGY OF SEPTIC LATERAL SINUS THROMBOSIS

| *Organism* | *Boston Series (4 Cases)* | *Literature (14 Cases)* |
|---|---|---|
| *Proteus* species | 1 | 6 |
| *Staphylococcus aureus* | 1 | 4 |
| *Escherichia coli* | 0 | 2 |
| *Bacteroides fragilis* | 2 | 0 |
| Anaerobic streptococci | 2 | 0 |
| Other | 2 | 3 |

Multiple organisms isolated from several cultures (included combination of *Bacteroides fragilis* and anaerobic streptococci). Modified from Southwick et al.[114]

of acute mastoiditis include fever, pain, swelling, and erythema of the mastoid area. Rarely, the mastoid tip cells perforate deep into the digastric muscle to form a Bezold's abscess.

Maharaj et al[122] evaluated the bacteriologic findings in 32 patients with acute mastoiditis; 6 patients' cultures yielded only anaerobes, and 22 (68.7%) patients had both aerobes and anaerobes. Organisms at Massachusetts Eye and Ear Infirmary have included *Peptostreptococcus*, *Clostridium*, and *Bacteroides* species. Brook[43] found similar organisms in chronic mastoiditis in children.

The patient with mastoiditis should be hospitalized and mastoid films and cultures of the middle ear obtained. Initial therapy might be intravenous cefuroxime until cultures are obtained. Two to 4 weeks of antibiotic therapy and wide myringotomy should suffice. If the bony partitions of the mastoid have eroded, then a complete mastoidectomy is necessary.

*Intracranial Complications of Acute Otitis Media*. The two major intracranial complications of acute otitis media include meningitis and lateral sinus thrombosis. (Meningitis will not be discussed in this paper.)

Pathophysiologically, the spread of infection to the lateral and sigmoid sinuses is from contiguous mastoid infection producing inflammation of the adventitia followed by penetration of the venous wall. In fact, most cases of lateral sinus thrombosis are now secondary to chronic otitis media rather than acute otitis media. The patient with lateral sinus thrombosis presents with ear pain, chills, and picket-fence fever. Tenderness to percussion over the mastoid emissary vein strongly suggests the diagnosis, which is confirmed on venous phase carotid angiography. Bacteriologic findings from the literature include *Proteus* (7 of 18 patients), *S aureus* (5 of 18), *E coli* (2 of 18), *Bacteroides fragilis* (2 of 18), and anaerobic streptococci (2 of 18 or 11%; Table 7[114]). Pallares et al[123] described a case with mixed organisms, and recently we also treated a 12-year-old patient with lateral sinus thrombosis and epidural abscess infected with *Fusobacterium necrophorum* at Massachusetts Eye and Ear Infirmary.

*Local Complications of Chronic Otitis Media*. The hearing loss that is the most frequent complication of this chronic ear infection is conductive and is reversible. Petrositis or Gradenigo's syndrome includes sixth nerve palsy and temporal-parietal pain from sensory fibers of the fifth nerve; this occurs following spread of infection from the mastoid along the ridge of the petrous bone, resulting in a small suppurative granuloma or abscess. Finally, facial paralysis also indicates similar pressure on the seventh nerve.

*Intracranial Complications of Chronic Otitis Media*. The mastoid is contiguous with the bone of the dura of the middle and posterior fossa; thus, chronic infection or granulation tissue or expansion of a cholesteatoma also allows access to the cranial contents[124,125] (Fig 5[124]). Intracranial complications include epidural abscess, brain abscess, and lateral sinus thrombosis.

Epidural abscesses are an uncommon complication, partly because extradural abscesses found incidentally in mastoid surgery are often excluded from the medical re-

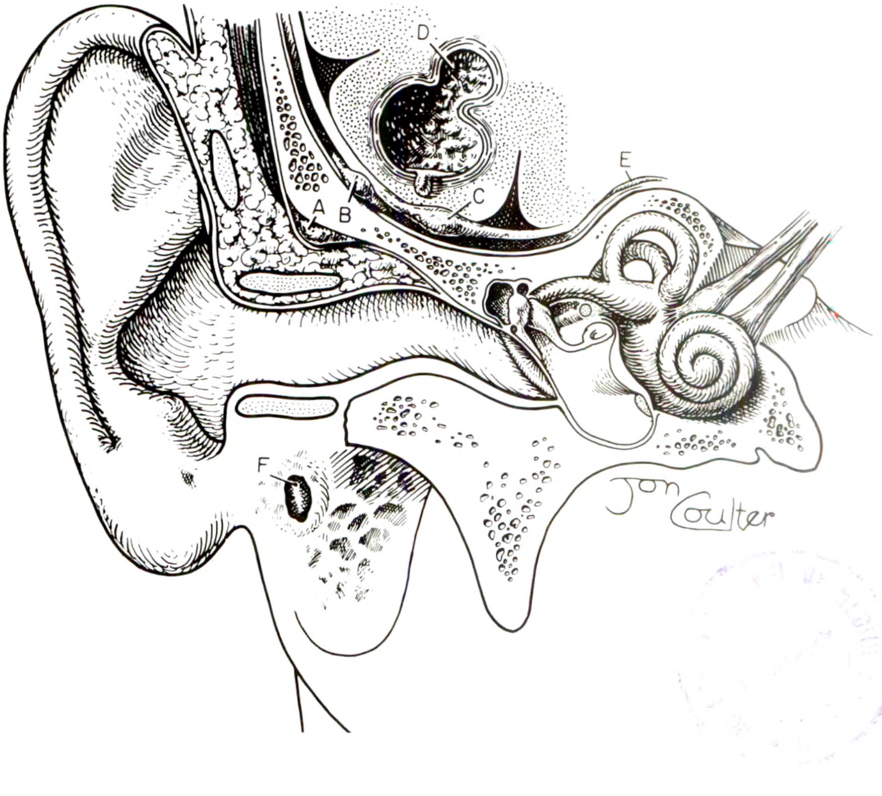


Fig 5. Suppurative complications of otitis media and mastoiditis. A — subperiosteal abscess, B — extradural abscess, C — subdural empyema, D — brain abscess, E — meningitis, F — lateral sinus thrombophlebitis. (Reprinted with permission.[124])

port. The dura is usually resistant to penetration unless infection spreads through the roof of the tympanic cavity as osteomyelitis and penetrates the dural and meningeal membranes to enter the temporal lobe of the brain.[126]

Otitic infections account for the largest number of brain abscesses; in a series of 154 cases due to anaerobes, 33% were secondary to otogenic factors.[127] The cardinal symptom of a brain abscess is headache. There may also be focal findings or signs of increased intracranial pressure. A CT scan with contrast is the procedure of choice; lumbar puncture should not be performed because of the risk of brain herniation.

Of 854 bacterial isolates from 436 patients, 46% were anaerobic. Ninety-two percent of these were peptostreptococci or anaerobic streptococci. The remaining 54% were facultative. There are two important generalizations to remember about the bacteriology of brain abscess: 1) the organisms differ from those causing meningitis; namely, streptococci, anaerobic and aerobic, are the most common organisms, as well as *Bacteroides*; and 2) anaerobic bacteria occur alone or in mixed groups in over one half of cases.[127]

Therapy includes aspiration of the abscess for cultures and treatment, high-dose intravenous antibiotics, surgical drainage (if feasible and necessary), steroids, and antiseizure medications.

Lateral sinus thrombophlebitis has been discussed under complications of acute otitis media.

## SUMMARY

Anaerobic bacteria comprise a major portion of the pathogenic bacteria in chronic sinus and ear infections, as well as the complications of these infections. Thus, therapy for frontal osteomyelitis, subdural abscess, orbital abscess, lateral sinus thrombosis, and brain abscess should include antibiotics that penetrate the central nervous system as well as cover anaerobic organisms. Penicillin, metronidazole, and chloramphenicol are three such agents.

# EXPERIMENTAL OTITIS MEDIA WITH ANAEROBIC BACTERIA

ROBERT S. FULGHUM, PHD; MARK E. BEAMER, MD

This report appears in partial form in the Proceedings of the International Conference on Acute and Secretory Otitis Media With Anaerobic Bacteria, Jerusalem, Israel, November 17-22, 1985 (Amsterdam, the Netherlands: Kugler Publications, 1986). This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of East Carolina University, Greenville, North Carolina.

One of the early references to the role of anaerobic bacteria in otitis media is found in the 1898 thesis by Rist,[128] who studied suppurative disease of the mastoid and middle ear as well as septicemia of otic origin, describing a number of cases including the bacteriology of the isolated organisms. Since the anaerobic method of the Paris Faculty of Medicine was difficult to perform although technically excellent, there were only sporadic reports of anaerobic isolates for the next 65 years (eg, Krumwiede and Pratt,[129,130] Busacca,[131] and Brisotto[132]). It was recognized, however, that otitis media could be the focus of infections metastasizing to other tissues. For example, Heineman and Braude[133] showed that chronic otitis media was the most probable origin of 8 of 18 cases of brain abscess. In the 1960s and early 1970s there were several retrospective studies reporting the isolation of such anaerobes as *Bacteroides* sp,[134,135] *Fusobacterium* sp,[136] anaerobic cocci,[134] and mixed cultures of both anaerobes and facultatively anaerobic bacteria[134] from cases of otitis media.

In 1977, two prospective studies reported the isolation of anaerobic bacteria from otitis media. Fulghum et al[137] studied fluid obtained by tympanocentesis from 10 patients of N. D. Fischer and W. P. Biggers. These patients were described to Fulghum as chronic otitis patients, but later examination of patient records showed them to have recurrent otitis media due in part to anatomic anomalies. Four of these cases yielded anaerobic bacteria: *Peptostreptococcus intermedius*, *Propionibacterium acnes*, and an unidentifiable gram-positive oval-shaped organism. These anaerobes were found in mixed culture with facultatively anaerobic and aerobic bacteria. Jokipii et al[93] studied 70 cases of chronic otitis media, finding anaerobes in 33% of these, almost always in mixed culture with aerobic and facultatively anaerobic bacteria. In these cases, most specimens yielded two anaerobic and two facultatively anaerobic species per specimen. Half of the anaerobic bacteria isolated were of the genus *Bacteroides*, and they were followed in frequency by species of anaerobic cocci, *Eubacterium*, *Fusobacterium*, *Clostridium*, and *Propionibacterium*. Further studies by Karma et al[49] confirmed and extended these observations. All three of these studies[49,93,137] speculated that synergistic action by the bacteria in the mixed cultures allowed the mixtures to have greater pathogenic potential in the middle ear than would any one of the members from the mixture.

Brook et al[38] in 1978 reported finding species of *Peptococcus* and *Propionibacterium acnes* in 9 of 62 patients with acute otitis media. They also found species of *Peptococcus*, *Eubacterium*, and *Propionibacterium acnes* in mixed culture specimens containing aerobic pathogens of acute otitis media in another 8 of the 62 patients. Ten patients had negative cultures from specimens, and the remaining 35 cultures contained pathogenic aerobic (or facultatively anaerobic) species of acute otitis media.

Brook and Finegold[41] in 1979 studied 50 patients with chronic otitis media having unperforated tympanic membranes. They found only aerobic and facultatively anaerobic bacteria in 21 patients (42%), only anaerobes (*Peptococcus* sp) in 3 (6%), and mixed cultures from specimens from 25 (50%) of the patients. Forty-eight anaerobes were isolated from these mixed culture specimens, including 24 gram-positive anaerobic cocci, 6 *Bacteroides melaninogenicus*, 4 *Bacteroides distasonis*, 3 *Bacteroides fragilis*, 3 *P acnes*, 2 *Fusobacterium nucleatum*, 2 *Bacteroides* sp, 1 *Bacteroides corrodens*, and 1 *Clostridium* sp.

Brook[138] reported the results of bacteriologic studies from 68 patients with chronic otitis media with perforated tympanic membranes, finding species of *Peptococcus*, *B fragilis*, *B melaninogenicus*, *B distasonis*, *F nucleatum*, *Bifidobacterium* sp, *Lactobacillus* sp, *Clostridium* sp, and *B corrodens* numerically in the order listed from exudate from the middle ears of 51% of these patients. Parallel studies were done to enumerate the species found in the exudate in the external auditory canal. The work showed the value of studying the exudate taken from the middle ear, since exudate from the canal may give misleading results.

In 62 of 720 cases of chronic otitis media, Sugita et al[50] in 1981 isolated 81 strains of anaerobic bacteria, including 32 strains of *Peptococcus* sp, 18 of *Bacteroides*, 6 of *Peptostreptococcus*, 6 of *Fusobacterium*, 5 of *Veillonella*, 4 of *Propionibacterium*, 3 of *Lactobacillus*, and 2 of *Clostridium*. These workers also reported the results of studies on the incidence of anaerobic bacteria in otitis media as found in 12 other studies over the period 1949 through 1977, showing that species of *Bacteroides* predominated numerically in these studies, followed by anaerobic cocci. Anaerobic gram-positive rods accounted for only 13% of the species isolated.

Luotonen et al[139] found anaerobic bacteria in only 1 of 71 middle ear aspirates of exudate from acute otitis media, while finding anaerobic bacteria in 11 ear canal samples. This outcome suggests that anaerobic bacteria play no significant role in acute otitis media. This work also suggests that contaminants from the ear canal may account for some of the anaerobic bacteria isolated from patients with acute otitis media.

Brook et al[39,42,67,69] have continued to refine these studies and to provide better data on the incidence of anaerobic bacteria in otitis media. Currently, these state-of-the-art studies indicate that the predominant anaerobic bacteria found in acute otitis media are mainly gram-positive cocci, many in mixed culture with other anaerobes and aerobes, and that they are found in about 25% of the cases studied. In serous otitis media, anaerobes are found in about 12% of the culture-positive aspirates; gram-positive anaerobic cocci and *B melaninogenicus* predominate among the anaerobes found, followed by *P acnes*. One half or more of patients with chronic otitis media yield aspirates from the middle ear containing species of anaerobic gram-positive cocci, *Bacteroides*, and *Fusobacterium*.

In studies of the bacteriology of cholesteatoma of the middle ear, about half of the cholesteatomas have been shown to involve anaerobic bacteria in large numbers, often mixed with aerobic and facultatively anaerobic species, both in humans[70,140,141] and in the gerbil.[142]

The role of β-lactamase–producing bacteria in the failure of treatments using the β-lactam antibiotics is an important consideration in the treatment of otitis media.[42] A number of anaerobic species found in otitis media are β-lactamase–producing organisms, as are a number of the aerobic and facultatively anaerobic bacteria found in middle ear infections. Production of β-lactamase by one member of a mixed-culture infection could protect other organisms in the infection that would otherwise be susceptible to β-lactam antibiotics.

Thore et al[143-145] have studied the effects of inoculating the guinea pig middle ear with species of anaerobes. The results of these studies were similar to those of Fulghum et al.[146] *Propionibacterium acnes* was found by Thore et al to produce otic infection comparable to that of *Streptococcus pneumoniae*, while *Peptostreptococcus micros* induced only a weak response. Although Thore et al state that *Bacteroides asaccharolyticus* produced no effects, this organism was used only in conjunction with *P micros* and not alone. Thore[144] showed that inoculation of *B fragilis*, *P acnes*, or *Peptostreptococcus anaerobius* into the middle ears of guinea pigs produced a mixed response in regard to antibody production. *Bacteroides fragilis* produced an early IgM and IgG serum antibody response, but little IgA. *Propionibacterium acnes* and *P anaerobius* produced no serum antibody response in the guinea pig. *Peptostreptococcus anaerobius* failed to produce sustained otitis media. In a study by Thore et al,[145] metronidazole was found to decrease the number of culture-positive ears that had been previously inoculated with *B fragilis*; however, the therapeutic efficacy was less than expected.

Beamer et al[147,148] used the Mongolian gerbil as an experimental animal to study the effects of anaerobic bacteria in the middle ear bulla. The Mongolian gerbil has been shown to develop otitis media with pathologic findings quite similar to those in humans when inoculated with the common etiologic agents of human otitis media: *Hemophilus influenzae*,[146,149,150] *S pneumoniae*,[146,150-152] *Pseudomonas aeruginosa*,[153] *Moraxella catarrhalis* (R. S. Fulghum and H. G. Marrow, unpublished data), and anaerobic bacteria.[146,148] The work with anaerobic bacteria in pure and in mixed cultures in the gerbil model is described in the Materials and Methods and Results sections of this report.

Also germane to consideration of the role of anaerobic bacteria in otitis media is information on the role of dead bacteria and degradation products of dead bacteria, such as cell wall components, which are difficult to eliminate biologically. Beamer et al[148] and Fulghum et al[150] have studied the effects of dead bacteria (also unpublished data) and of cell wall (peptidoglycan) fragments, muramyl peptides, and peptides from peptidoglycan on the middle ear mucosa (unpublished data). All of these substances produce middle ear inflammation. The importance of these findings relative to the finding of anaerobic bacteria in otitis media is treated in the Discussion section of this report.

TABLE 8. SPECIES OF BACTERIA USED IN STUDIES OF EXPERIMENTAL OTITIS MEDIA

| *Species* | *Strain Designation* | *Source* |
|---|---|---|
| *Escherichia coli* | ATCC 11303-4 | ? |
| *Bacteroides fragilis* | Pitt County Memorial Hospital Laboratory | Clinical ? |
| *Bacteroides melaninogenicus* | 536, Brook and Finegold | Otitis media |
| *Fusobacterium nucleatum* | ATCC 10953 | ? |
| *Clostridium perfringens* | Centers for Disease Control | ? |
| *Gaffkya anaerobius* | Brook and Finegold | Otitis media |
| *Peptococcus magnus* | Brook and Finegold | Otitis media |
| *Peptostreptococcus anaerobius* | ATCC 27337 | ? |
| *Peptostreptococcus intermedius* | Fulghum, Daniel, and Yarborough | Otitis media |
| *Propionibacterium acnes* | Fulghum, Daniel, and Yarborough | Otitis media |

The present report is a preliminary study of the effects of anaerobic bacteria in experimentally caused otitis media.

## MATERIALS AND METHODS

The materials and methods used in this study are described in the literature.[146-153] The Mongolian gerbils were housed and maintained under optimum laboratory animal care conditions. Animals were anesthetized with a mixture of ketamine and xylazine. All animals were examined otoscopically[150] before use to ensure using only animals with healthy ears. Inoculum preparation and inoculation procedures were as described previously as per cutaneous inoculation directly into the middle ear bulla.

Table 8 shows the species of bacteria used in this study and the sources of these organisms. All cultures were recharacterized in our laboratory by the methods of the VPI & SU Anaerobe Laboratory.[154] The organisms were maintained in anaerobic chopped meat medium[154] and were grown in peptone yeast extract glucose medium[154] until logarithmic growth was achieved. These cultures were then diluted to one half of a No. 1 McFarland turbidity standard, resulting in approximately $1.5 \times 10^8$ cells per milliliter of cell suspension. For inoculation, 0.03 mL of the suspension was used, resulting in delivery of approximately $4.5 \times 10^6$ cells per ear. Right ears were inoculated, the left serving as uninoculated controls. Polymicrobial mixtures were grown and diluted as above. Equal volumes of each species to be used were mixed, and 0.03 mL of the mixture delivered approximately $4.5 \times 10^6$ of the mixed cells to each ear inoculated.

Behavioral and otoscopic observations were made at intervals of 3, 5, 7, 14, 21, and 28 days. At each examination period, at least one animal was killed painlessly, perfused, fixed with tissue fixative, and decapitated. The heads were decalcified, embedded in paraffin, and sectioned coronally, and selected sections were stained with hematoxylin and eosin. The pathologic findings on these sections were described and graded

TABLE 9. PATHOLOGY GRADE ACHIEVED BY INDIVIDUAL SPECIES

| *Microorganism Inoculated* | *State* | *Maximum Grade Achieved** | *Days Following Inoculation to Achieve Maximum Grade* |
|---|---|---|---|
| *Escherichia coli* | V | 5 | 5 |
| | N | 4 | 5 |
| *Bacteroides fragilis* | V | 5 | 28 |
| | N | 5 | 14 |
| *Bacteroides melaninogenicus* | V | 5 | 14 |
| | N | 2 | 3 |
| *Fusobacterium nucleatum* | V | 4 | 3 |
| | N | 4 | 5 |
| *Clostridium perfringens* | V | 5 | 21 |
| | N | 4 | 5 |
| *Gaffkya anaerobius* | V | 2 | 5 |
| | N | 2 | 5 |
| *Peptococcus magnus* | V | 2 | 5 |
| | N | 1 | 5 |
| *Peptostreptococcus anaerobius* | V | 5 | 7 |
| | N | 4 | 7 |
| *Peptostreptococcus intermedius* | V | 4 | 5 |
| | N | 5 | 5 |
| *Propionibacterium acnes* | V | 2 | 3 |
| | N | 5 | 14 |

V — viable, N — nonviable.

*See text (Methods).

A grading scale of 1 to 5 that considered 1) amount of exudate and phagocytic cells, 2) bone resorption or new bone formation, and 3) elevation of the mucoperiosteum (MPO) was devised for numeric evaluation of pathologic changes.[148] Scoring these changes was carried out as follows. Three chambers of the middle ear of each gerbil were examined for amount of exudate containing polymorphonuclear leukocytes (PMNs) and scored from 0 (no exudate) to 8 (all three chambers plus more than half of the entire bulla filled with exudate containing PMNs). The MPO of the entire periphery of the bulla shown in the histologic specimen was examined and scored from 0 (no changes) to 4 (periosteum thickened, vascularized, and elevated). The bone of the bulla was examined for changes — either bone resorption or new bone formation — and scored from 0 (no change) to 8 (new bone formation around more than half of the perimeter of the bulla). The scores from each of these categories were added and the final grade of pathologic changes was determined by using the following: a score of 0 to 1 was grade 0, a score of 2 to 4 was grade 1, a score of 5 to 7 was grade 2, a score of 8 to 10 was grade 3, a score of 11 to 14 was grade 4, and a score of 15 or more was grade 5.

A separate study of each histologic section from this study was made by one of us (R.S.F.) in which each section was scored as plus or minus for exudate, plus or minus for elevation of the MPO, plus or minus for appearance of granulation tissue, and plus or minus for bone changes. Concise notes were made regarding the extent of plus findings in each category. In addition, the numbers of PMNs and macrophages were counted in three 0.00016-$cm^2$ areas of exudate (one field of our 100x oil immersion lens), averaged, and recorded.

TABLE 10. PATHOLOGY GRADE ACHIEVED BY POLYMICROBIAL INOCULA

| *Polymicrobial Inoculum** | *Maximum Grade Achieved†* | *Days Following Inoculation to Achieve Maximum Grade* |
|---|---|---|
| *B fragilis* and *F nucleatum* | 3 | 3 |
| *B fragilis* and *E coli* | 5 | 7 |
| *B melaninogenicus* and *E coli* | 5 | 7 |
| *B fragilis* and *P intermedius* | 5 | 14 |
| *B melaninogenicus* and *P magnus* | 4 | 3 |
| *F nucleatum* and *P intermedius* | 3 | 5 |
| *C perfringens* and *P magnus* | 5 | 7 |
| *C perfringens* and *P acnes* | 5 | 7 |
| *P acnes* and *P intermedius* | 3 | 5 |
| *P anaerobius* and *P magnus* | 3 | 3 |
| *B fragilis*, *B melaninogenicus*, and *P acnes* | 5 | 5 |
| *B fragilis*, *E coli*, and *P intermedius* | 5 | 5 |
| *B melaninogenicus*, *P anaerobius*, and *P magnus* | 5 | 14 |
| *B melaninogenicus*, *P anaerobius*, and *P intermedius* | 4 | 14 |
| *C perfringens*, *P intermedius*, and *P acnes* | 5 | 7 |

*Total number of cells in all mixtures = $4.5 \times 10^6$. See Methods.

†See text (Methods).

## RESULTS

Comparison of the results of the two evaluations of histopathology seen in each section studied in this work showed that the evaluations were comparable, although evidence of permanent sequelae not well represented by the earlier scoring system was found in the later study. The results in Tables 9 and 10 were from the earlier evaluation.

Table 9 summarizes the results of inoculating living and heat-killed pure cultures of selected species of anaerobic bacteria into the middle ears of gerbils. With the exception of *Gaffkya anaerobius* and *Peptococcus magnus*, all of the organisms produced maximum pathologic changes (similar to that produced by *Streptococcus pneumoniae* in other studies)[146,151] or near-maximum pathologic changes characterized by an exudate that contained immature and mature PMNs as the predominant cells during the first 5 days following inoculation. In the period following the fifth day, mature and immature macrophages predominated in exudates. All organisms and mixtures of organisms were able to cause an elevated, sometimes thickened and vascularized MPO in the gerbil middle ear. These changes were evident at our earliest histologic examinations (day 3 following inoculation) and in all animals studied. Five to 7 days following inoculation, areas of granulation tissue growing from the MPO were evident with all organisms except *G anaerobius* and *P magnus*. In general, development of granulation tissue in this study with anaerobes was more rapid than seen with organisms such as *S pneumoniae* and *H influenzae* in our earlier studies. Similarly, bone changes including formation of new bone appeared earlier with the anaerobic inocula used in this study.

In this study, we directly compared the anaerobic species with *Escherichia coli*, as it has been shown to produce pathologic changes and to be synergistic with anaerobic bacteria in producing pathologic changes.[155] *Escherichia coli* alone produced maximum pathologic changes within 5 days. The range of time to produce maximum pathologic

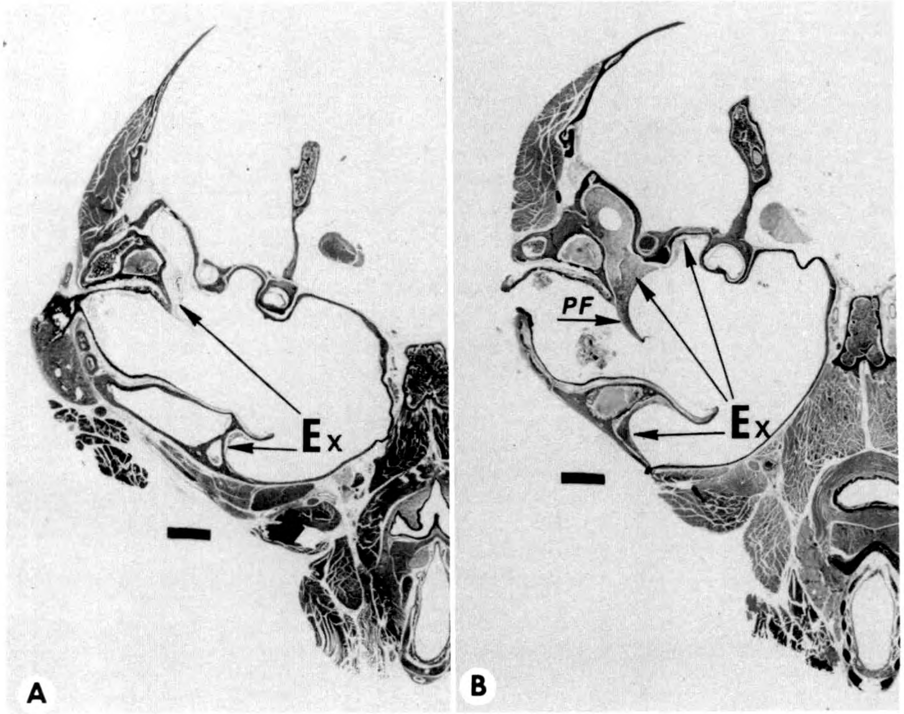


Fig 6. A) Coronal cross section of gerbil bulla showing exudate (Ex) containing polymorphonuclear leukocytes in two chambers of bulla. Mucoperiosteum under exudate is elevated. No changes in bone are found. B) Exudate containing polymorphonuclear leukocytes is found within three chambers. Exudate extends from one chamber into middle ear cavity, covering pars flaccida (PF). There is elevation of mucoperiosteum; however, there are no changes in bone. Bars — 1 mm. (Modified with permission.[148])

changes with the anaerobic species was from 7 to 28 days, depending upon species and whether living or heat-killed. *Escherichia coli* and *P anaerobius* established infections leading to grade 5 (permanent sequelae) within 7 days. *Bacteroides melaninogenicus* established grade 5 infections within 14 days, while *B fragilis* and *Clostridium perfringens* required nearly 4 weeks. Among heat-killed cultures, *B fragilis* was the only organism to produce a consistent grade 5 response. *Propionibacterium acnes* produced a greater response as a heat-killed culture than as a living culture in this study.

Table 10 contains the results of inoculating two- and three-culture mixtures of selected anaerobic bacteria or of anaerobic species and *E coli*. In these studies, the total number of cells in the mixtures was the same as in the single-culture experiments: 4.5 x $10^6$ cells per inoculation. *Bacteroides melaninogenicus* and *E coli* displayed the greatest pathologic changes among the two-culture mixtures. Some of the mixed cultures achieved maximum pathologic changes more rapidly than did the component pure cultures, eg, with *P acnes* and *C perfringens* and with *B fragilis* and *P intermedius*. Most of the remaining mixed cultures achieved a grade of pathologic changes similar to that of the most pathogenic organism of the mixture. In several mixtures, it appeared that the mixture was not as pathogenic as the most pathogenic member of the mixture; thus, some organisms appear to limit pathogenicity of another in mixed culture.

While the mixture of *E coli*, *B fragilis*, and *P intermedius* achieved the highest grade of pathologic changes among the three-culture mixtures, synergy of pathogenicity seemed to be found only in the mixture of *B melaninogenicus*, *B fragilis*, and *P acnes*. The mixture of *P intermedius*, *P anaerobius*, and *B melaninogenicus* showed the lowest grade of infection, with presumed antagonism among these organisms reducing pathogenicity.

Figure 6[148] shows coronal cross sections through the right gerbil middle ear bulla. Figure 6A shows the gerbil bulla with a grade 1 infection. Small amounts of exudate may be seen in two of the chambers of the bulla. These exudates contain PMNs, although they cannot be seen at the magnification of this photomicrograph. Areas of mucoperiosteal thickening are present under the exudate and at other locations in the bulla. No changes in the temporal bone are seen in this specimen. The changes seen here are scored as follows: exudate with PMNs, 2; MPO, 1; bone, 0. The total score equals 3, which is equivalent to a grade 1 infection.

Figure 6B shows an example of a grade 3 infection. Here, three chambers of the bulla are found to contain exudate with PMNs. The contents of one chamber have filled the chamber and extend across the pars flaccida of the tympanic membrane. The histopathologic changes seen here are scored as follows: exudate with PMNs, 6; MPO, 2; bone, 0. The total score equals 8, which is equivalent to a grade 3 infection. While caused by a different species of bacterium, these histologic changes are similar to those seen in Fig 6B, except that here no bone changes are seen and the involvement is not as extensive within the bulla in the present figure. Figures 7 and 8 document these changes, which were typical of the majority of our acute infections caused by anaerobes or mixtures of anaerobes used in this study. Figure 7 shows at two magnifications the elevation and vascularization of the MPO of gerbils inoculated with *B fragilis* 2 days prior to killing. The exudate contains predominantly PMNs in addition to red blood cells from the bloody exudate. Figure 8 shows a section from a gerbil inoculated 7 days prior to killing and depicts continued elevation and vascularization of the MPO. Macrophages were counted and represented two thirds of the phagocytic cells in the exudate, although this distribution of cells is not seen in the photomicrograph.

Figure 9[148] depicts grade 5 infections. Figure 9A represents a grade 5 infection in the acute phase. Note that the entire bulla is filled with exudate containing PMNs. The entire MPO is elevated. Areas of deposition of cancellous bone are seen. The histopathologic findings are scored as

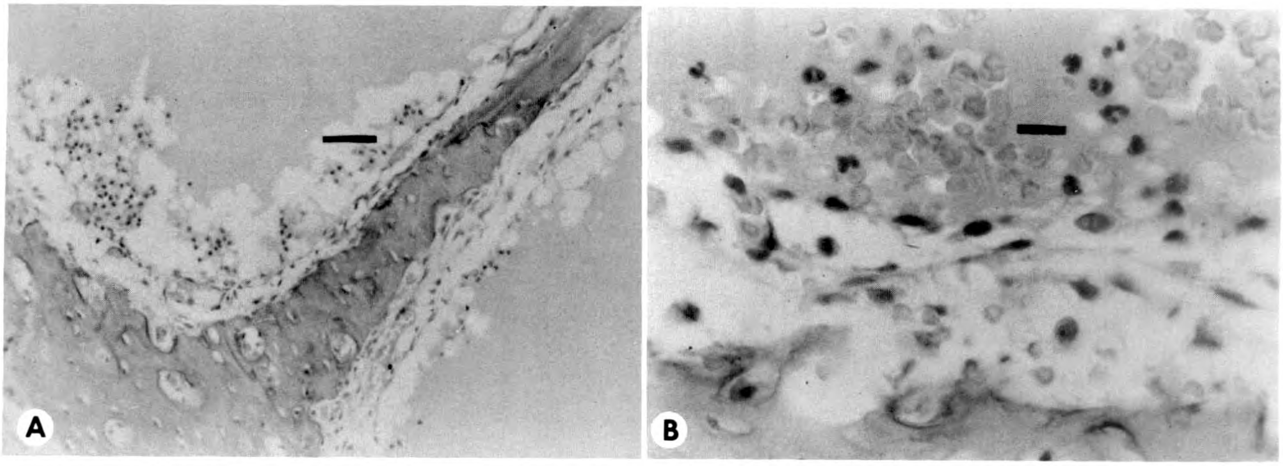


Fig 7. Elevation and vascularization of mucoperiosteum with copious exudate containing polymorphonuclear cells 2 days following inoculation of gerbil middle ear with *Bacteroides fragilis*. A) Original x100. Bar — 10 μm. B) Original x400. Bar — 50 μm.

follows: exudate with PMNs, 8; MPO, 4; and bone, 6; for a total score of 18. Figure 9B is a photomicrograph of a grade 5 chronic infection. The exudate is replaced by a vascular granulation tissue that extends from the MPO. This granulation tissue is more likely to contain plasma cells and macrophages than PMNs. Considerable new bone formation is seen and part of the cancellous new bone laid down earlier in the infection has become more dense. These histologic changes are similar to those shown in Figs 7 through 11. Fig 10A shows granulation tissue and some exudate surrounding the malleus of a gerbil inoculated 7 days earlier with a mixture of *C perfringens*, *P acnes*, and *P intermedius*. Figure 10B shows cancellous new bone and the MPO thickened into granulation tissue caused by inoculation of *B fragilis* 14 days earlier. For comparative purposes, Fig 11 shows new bone and granulation tissue produced by inoculation of a mixture of *B fragilis* and *P intermedius* 14 days previously.

Mixed-culture inoculations produced histologic changes in gerbils similar to those found in chinchillas inoculated with a mixed-infection flora. Details of these changes are shown in Fig 8 and in an earlier publication[146] from our laboratory.

## DISCUSSION

The histopathologic changes of anaerobic infections induced in the middle ear of the gerbil and the sequelae of these infections within the middle ear do not differ greatly among the various etiologic agents that we have used in this and in previous studies,[146,149,151,152] except in degree of changes, which varies among pneumococcal types, *H influenzae* types, and the various anaerobes and mixtures of anaerobes and aerobes. In general, we found in the present study that all cultures of anaerobes and mixtures used elicited an exudate that contained immature and mature PMNs as the predominant cells during the first 5 days following inoculation. In the period following the fifth day, immature and mature macrophages predominated in exudates. All organisms and mixtures of organisms were able to cause an elevated, sometimes thickened and vascularized MPO in the gerbil middle ear. These changes were evident at our earliest histologic examinations (day 3 following inoculation) and in all animals studied. Five to 7 days following inoculation, areas of granulation tissue growing from the MPO were evident in many specimens. In general, this was a more rapid development in this study with anaerobes than seen with organisms such as *S pneumoniae* and *H influenzae* in our earlier studies.[146,149,152] Similarly, bone changes, including formation of new bone, appeared earlier with the anaerobic inocula used in this study. More than likely, this early appearance of chronicity (macrophage predominance, granulation tissue, and bone change) was due to the larger numbers of

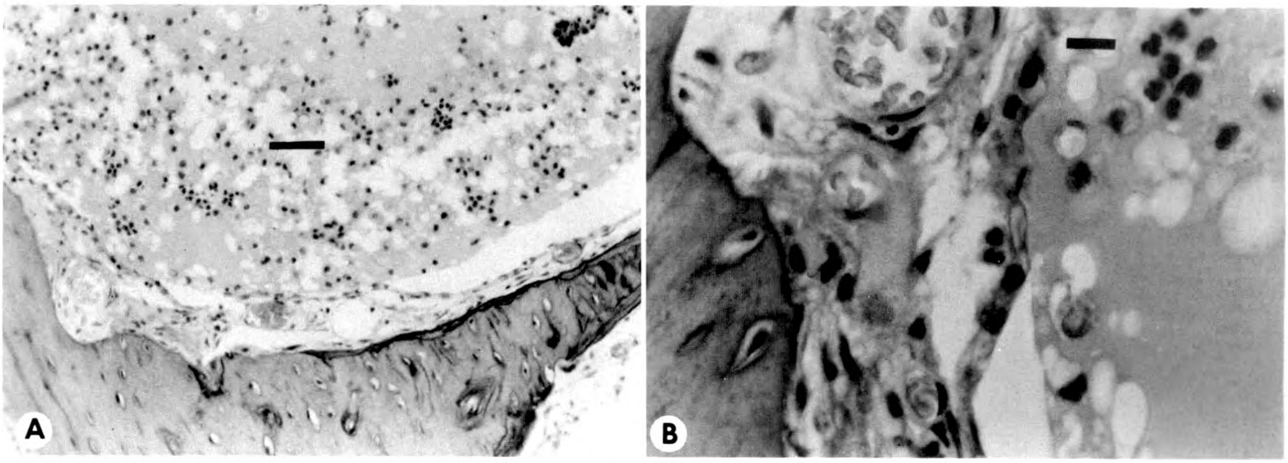


Fig 8. Elevation and vascularization of mucoperiosteum with copious exudate containing predominantly macrophages 7 days following inoculation of gerbil middle ear with *Bacteroides fragilis*. A) Original x100. Bar — 10 μm. B) Original x400. Bar — 50 μm.

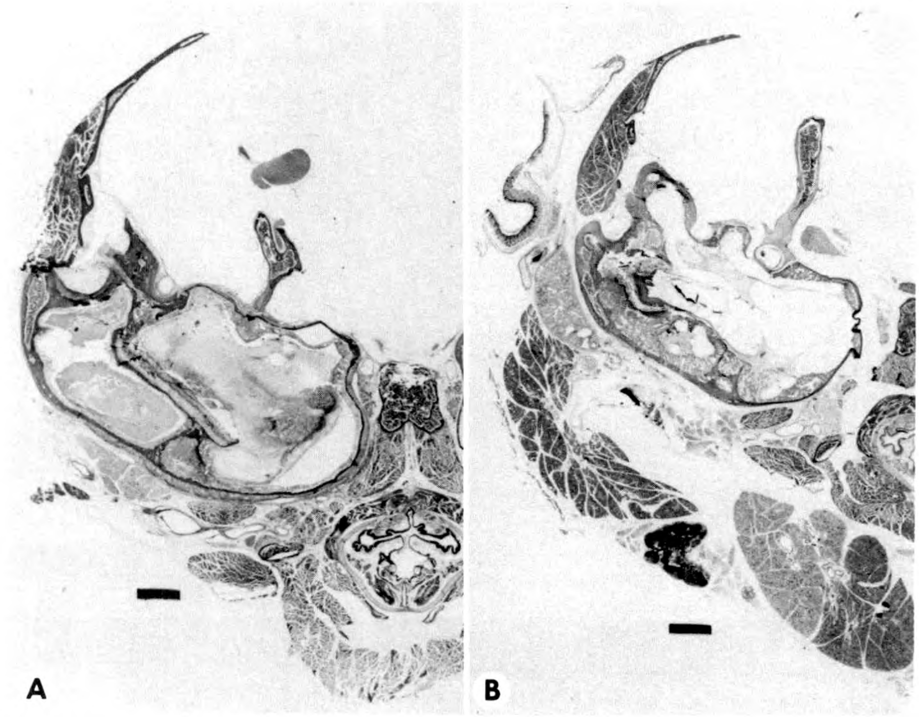


Fig 9. A) Coronal cross section of gerbil bulla showing exudate filling all chambers as well as bulla. Mucoperiosteum is elevated and small amount of cancellous bone is laid down. This is typical of acute infection at about 1 week following inoculation. B) Exudate has been replaced with vascular granulation tissue. Considerable new cancellous bone is seen, as well as formation of new, more dense bone. This is typical of sequelae of untreated otitis media after 3 weeks following infection. Bars — 1 mm. (Modified with permission.[148])

bacterial cells inoculated in the present study.

In regard to the degree of histopathologic changes as presented by our grading scheme and the time of incubation to maximum pathologic changes elicited by each species and mixture, our present results must be cautiously interpreted, because we used a survey type of longitudinal study in which only one animal was killed per incubation period. Further work with these organisms and mixtures of organisms must be performed with appropriate numbers of animals to more accurately document the range and course of the otitis media produced.

Granulation tissue and new bone formation have been shown to be hallmarks of untreated infection in the bulla of guinea pigs and in the mastoid air cells of humans,[155] as well as in gerbils[146,149,151] and chinchillas.[150] Paparella et al[156] have shown the sequelae of chronic otitis media in human adults to include the irreversible changes of granulation tissue, cholesteatoma, cholesterin granuloma, osseous changes, subepithelial fibrosis, and fibrous adhesions. It is not known whether these changes are due to living organisms or are due to dead bacteria, components (cell wall parts, endotoxin, etc) of disintegrating dead bacteria, or the products of phagocyte killing released into the middle ear. The work of Brook[157] and others (eg, Okazaki et al[158]) has shown the importance of the capsule of anaerobic bacteria as a pathogenic factor. Undoubtedly, our observation that heat-killed *B fragilis* causes as much damage as the living culture is due to the presence of capsule of *B fragilis*. Several studies[159-161] have shown that dead bacteria and bacterial cell components are able to cause inflammation in experimental animals. Our work[151,152] (and unpublished data) confirms these studies by using the gerbil model inoculated with cell wall fragments (peptidoglycan), muramyl peptides, and peptide cross-linking bridges from peptidoglycan, all of which caused otitis media. Inflammation due to dead cells or components thereof not only causes otitis media but also may predispose the mid-

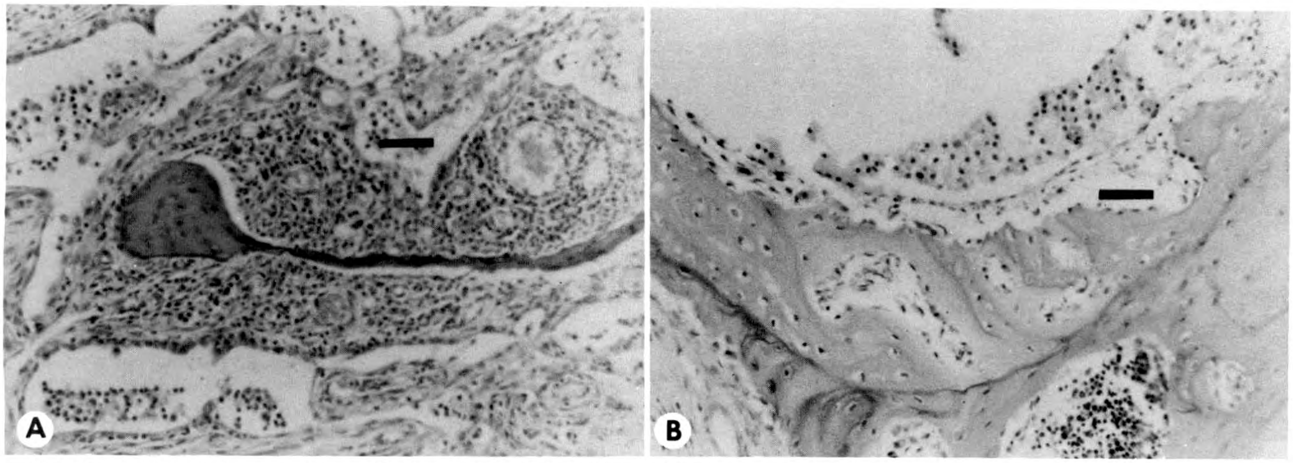


Fig 10. Sequelae of chronic otitis media due to inoculation of anaerobic bacteria. Bars — 10 μm. A) Granulation tissue surrounding malleus of gerbil inoculated 7 days previously with mixture of *Clostridium perfringens*, *Propionibacterium acnes*, and *Peptostreptococcus intermedius*. B) Granulation tissue and new bone produced as sequelae of inoculation of *Bacteroides fragilis* 14 days earlier.

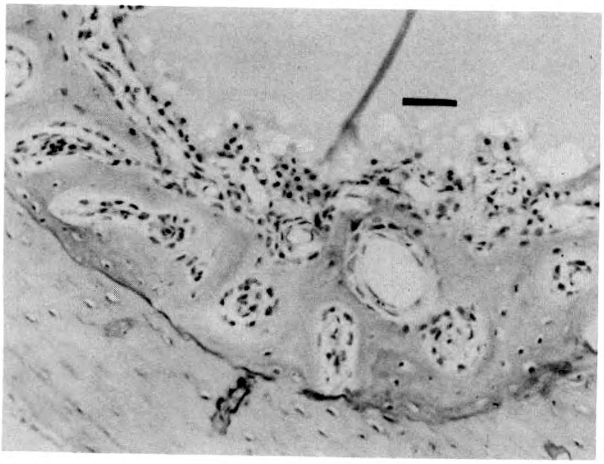


Fig 11. Cancellous new bone and granulation tissue resulting from inoculation 7 days previously of *Bacteroides fragilis* and *Peptostreptococcus intermedius* into middle ear of gerbil. Bar — 10 μm.

dle ear to reinfection by less pathogenic organisms that in turn may exacerbate sequelae already in place. Since peptidoglycan is difficult to degrade and eliminate biologically, the continued presence of these bacterial products in the middle ear could be one factor in the development of recurrent or chronic otitis media.

We have not attempted to correlate the histopathologic changes found in our present study with any one species of bacterium or with any polymicrobial mixture of bacteria, since the results are very similar for most experimental infections in these animal models, the histopathologic changes varying only in degree of severity with most of the organisms used. Further studies are necessary in this area to document the range of changes produced by each organism and each mixture of organisms at various times following inoculation. These studies should include painless killing and histopathologic study of at least five animals at each time of killing for each species and mixtures of species.

Synergy[66,162] and inhibition may be a feature of polymicrobial middle ear infections; however, our present work does not well document these facets of polymicrobial infection, and further studies are needed to answer these questions. Further work is also necessary to determine whether it is the living organism or bacterial components from dead bacteria that is the primary cause of pathologic changes in anaerobic experimental infections. The question of minimum infective dose of polymicrobial anaerobic infections needs to be addressed.

In summary, we have presented preliminary data on the severity of experimental infection of the gerbilline middle ear bulla using pure and polymicrobial cultures of anaerobic bacteria, and have described a system of scoring the pathologic changes and grading the infections.

# ROLE OF ANAEROBIC BACTERIA IN INFECTIONS OF THE TONSILS AND ADENOIDS

SYDNEY M. FINEGOLD, MD

It is clear that anaerobic bacteria are involved in both acute and chronic/recurrent infection of the tonsils, although there is little direct evidence of this. The evidence chiefly derives from studies of complications of anaerobic tonsillitis (Table 11) such as bacteremia and local extension, including peritonsillar abscess and various neck space infections. There is remarkably little information from any source on the role of anaerobes in infection involving the adenoids. There has also been interest in the possibility that production of β-lactamases by anaerobic bacteria in or near the tonsils may influence therapy of group A streptococcal pharyngitis.

## ROLE OF ANAEROBES IN INFECTION OF TONSILS AND ADENOIDS

*Acute Tonsillitis.* Although most cases of acute tonsillitis involving anaerobes are undoubtedly overlooked at present, in its classic form this process is very distinctive. Anaerobic tonsillitis or tonsillopharyngitis, also known as Vincent's angina, is characterized by superficial ulceration and necrosis often resulting in formation of pseudomembrane. There is typically a foul odor to the breath, and there may be a foul discharge noted. Often there is submandibular lymph node enlargement. In the antibiotic era the vast majority of patients are undoubtedly treated early and never progress to the classic picture just described. In addition, however, many cases — even before antimicrobials were available — were quite mild in terms of the local expression in the tonsils and yet might be complicated by serious sepsis and metastatic infection (postanginal sepsis [Lemierre's disease]). Studies of patients with postanginal sepsis indicate that the primary pathogen in tonsillitis is *Fusobacterium necrophorum*. This organism has been isolated from blood cultures and from sites of metastatic infection on innumerable occasions, although other organisms may sometimes be recovered (see later discussion of this disease process).

Most acute anaerobic tonsillar infections are of endogenous origin, but there may be transmission from person to person through intimate contact, such as kissing, or even by means of shared towels or toothbrushes.[163]

The differential diagnosis of Vincent's angina includes group A β-hemolytic streptococcal infection, nonstreptococcal exudative pharyngitis (viral), infectious mononucleosis, and diphtheria. It should be remembered that anaerobic tonsillopharyngitis may coexist with these other diseases.

Brook and Gober[76] suggested that organisms belonging to the pigmented *Bacteroides* (which would now also include *Prevotella* or *Porphyromonas*) may play a pathogenic role in acute tonsillitis in children. They recovered encapsulated organisms of these types from 23 of 25 children with tonsillitis as compared with 5 of 23 control patients; furthermore, they found on subcutaneous inoculation of these strains into mice that those isolated from patients with tonsillitis were more likely to produce abscesses than were strains isolated from the control patients. Certainly, much more study is required before we can accept these organisms as causes of tonsillitis.

There is also a report[164] in which group F streptococci (*Streptococcus anginosus*) were isolated in moderate to heavy growth from a number of children and adolescents with symptomatic pharyngitis. In most cases anaerobic techniques were required for recovery of these β-hemolytic organisms. There is reason to consider that these organisms might be classified as anaerobes.[35] Certainly, additional studies, including comparison of isolation rates of these organisms from a control population of well children, will be required before these organisms can be considered to play a role in pharyngitis or tonsillitis.

*Chronic or Recurrent Tonsillitis.* As in acute tonsillitis, most of the evidence of involvement of anaerobic bacteria in chronic or recurrent disease is indirect. There is one report[165] in which a 16-year-old patient with tonsillitis and cervical adenitis of 2 months' duration had surgical drainage. The purulent material that was recovered grew *Peptostreptococcus* and a *Bacteroides* species.

Brook et al[54] did bacteriologic studies on 1 tonsil each from 50 children undergoing tonsillectomy. The tonsil was cauterized and an incision was made through that area, cutting the tonsil in half; the core of the tonsil was then swabbed for aerobic and anaerobic culture. There were a total of 207 anaerobic organisms and 185 aerobic and facultative bacteria recovered. The predominant anaerobes were *Bacteroides*, including 47 isolates of pigmented *Bacteroides* and 12 of the *Bacteroides fragilis* group; also prevalent were *Peptostreptococcus* species and *Fusobacterium* species, particularly *Fusobacterium nucleatum*. Among the aerobic and facultative bacteria, gram-positive cocci dominated, with viridans streptococci accounting for 41% of the isolates and *Staphylococcus aureus* 24%. There were 25 isolates of *Neisseria* species. A later study from this group[166] involved bacteriology of tonsillar cores from 22 patients (1 tonsil each). The results were similar to those reported in the earlier study; however, on this occasion pigmented organisms that would now be classified as *Prevotella* or *Porphyromonas* were also recovered. Mann and Pelz[167] did a similar study with anaerobic culture of 30 tonsils of patients with chronic infection. The bacteriologic data were much like those reported by Brook's group. There were a total of 5 isolates of the *B fragilis* group in the Mann and Pelz study.

TABLE 11. COMPLICATIONS OF ANAEROBIC TONSILLAR INFECTIONS

Adenitis, edema, trismus

Thrombophlebitis of tonsillar, peritonsillar, facial, and internal jugular veins

Bacteremia; metastatic infection (brain, lung, pleural space, liver, joints, bone, muscle, etc)

Local extension
- Peritonsillar abscess
- Parapharyngeal abscess, retropharyngeal abscess
- Other neck space infection

Two studies[55,168] demonstrated the superiority of culture of the tonsillar core as compared with surface swabbing of tonsils with regard to the numbers of organisms recovered, particularly anaerobes.

A paper by Brook[169] reports that from 10% to 20% of specimens from chronic infections and abscesses from Waldeyer's ring yield members of the *B fragilis* group. This paper also notes that fusobacteria are recovered from chronically inflamed adenoids, as well as tonsils. A study by Povolotskii et al[170] noted recovery of anaerobic streptococci from 100% of tonsillar tissue samples and 61% of tonsillar swabs. Other anaerobic organisms, as well as nonanaerobes, were recovered, but anaerobic streptococci were noted to be among the most common. These authors also demonstrated that sera of patients with chronic tonsillitis or paratonsillitis exhibited antibodies to the anaerobic streptococci that were isolated significantly more often and in significantly higher titer than did sera from normal persons.

Two other studies[171,172] failed to recover anaerobes from adenoid tissue and tonsils. These results must be questioned in light of the data already presented.

The causative agents of actinomycosis have been recovered with some frequency from resected tonsils.[173] *Actinomyces* and *Arachnia* have also been isolated from infections related to the tonsils.[35,174]

*Role of Anaerobes as "Copathogens" in Infection of Tonsil.* The possibility exists that there may be mixed anaerobic-aerobic infections of the tonsil, but this is impossible to study in the absence of an experimental model. The nature of anaerobic infections elsewhere in the body, however, does support this notion.

It has been suggested[58,82,175,176] that β-lactamase–producing anaerobes (and aerobes) may contribute to failure of penicillin to eradicate group A β-hemolytic streptococci — a factor that could account for recurrent infections and, perhaps, treatment failures. This is discussed in greater detail elsewhere in this symposium.

## COMPLICATIONS OF ANAEROBIC TONSILLITIS

*Minor Local Complications.* As indicated earlier, anaerobic tonsillitis may be complicated by periadenitis and suppurative adenitis.

*Thrombophlebitis.* As a complication of anaerobic tonsillar infection, one may get thrombophlebitis of the tonsillar, peritonsillar, facial, and internal jugular veins. By far the most important clinically is septic thrombophlebitis of the internal jugular venous system. In essence, this is part of the picture of postanginal sepsis, which will be discussed in the next section of this manuscript; however, it is well to consider it as a separate entity for emphasis. Symptoms of jugular vein thrombosis include pain on the side of the neck and on movement of the neck away from the side involved. This motion involves contraction of the sternocleidomastoid muscle, which compresses the inflamed mass. Pain and swelling may be seen at the angle of the jaw; there may be facial swelling and swelling about the eye. There is tenderness and induration along the overlying sternocleidomastoid muscle, and a palpable cord deep to the muscle may be appreciated. There may be dysphagia and hoarseness, and it may be possible to note edema of the vocal cord on the involved side, as well as edema of the false vocal cords, the arytenoid, and the lateral pharyngeal wall. Swelling of the lateral portion of the neck is seen frequently. The thrombosed vein may not be palpable in the neck because of swelling. It should be realized also that the local findings of jugular venous thrombosis may be subtle and overlooked easily. In the preantimicrobial era, when this process was considerably more common, it is estimated that the condition was recognized antemortem in only 20% of cases.

TABLE 12. CLINICAL PICTURE OF POSTANGINAL SEPTICEMIA (LEMIERRE'S DISEASE)

| |
|---|
| Primarily in children; may be seen in young adults |
| Tonsillopharyngitis |
| Inapparent |
| Mild to severe; may have exudate (pseudomembrane), ulceration, foul odor |
| May have subsided prior to onset of sepsis |
| Septic thrombophlebitis, especially of internal jugular vein (may have palpable cord) |
| Fever, rigors |
| Pain, swelling at angle of jaw |
| Facial and eye swelling |
| Tenderness along overlying sternocleidomastoid muscle |
| Swelling of lateral pharyngeal wall |
| Dysphagia |
| Stiff neck |
| Jaundice |
| Evidence of metastatic infection (septic embolization) |

Ultrasonography and axial computed tomography (CT) may help identify the process in the jugular vein. Contrast-enhanced axial CT scanning may show enhancement of the normal carotid and an enlarged jugular venous wall surrounding a more lucent intraluminal clot. Retrograde venography may also identify a clot in the jugular vein, but is unnecessarily invasive.

Antimicrobial agents are the key to successful therapy; this is outlined in the next section, on postanginal sepsis. The issues of anticoagulation and surgical intervention are difficult ones. Anticoagulation is certainly not required in all cases, but on occasion it seems to have made an impressive difference in terms of the response of the patient.[177] There is a risk of hemorrhage related to erosion of the carotid artery, which is located in close proximity. Surgery should be reserved for patients who continue to run a febrile course or who give evidence of septic embolization despite optimal medical therapy. In such cases, neck exploration with surgical ligation may be curative.[177]

*Postanginal Sepsis.* The distinctive clinical picture of this entity is outlined in Table 12. The underlying tonsillopharyngitis varies greatly in severity, from a very mild illness to severe exudative disease with ulceration and foul odor. In a number of cases there has been no recollection of sore throat by the patient or any evidence on physical examination that the patient has actually had tonsillopharyngitis, in spite of developing the classic picture of postanginal sepsis. Also, there may be an interval between apparent recovery from the tonsillopharyngitis and the onset of the severe picture of sepsis. Septic thrombophlebitis of the internal jugular vein, which may be an important part of this picture, has been described in the previous section. As noted there, the manifestations of jugular thrombophlebitis may be relatively minor and may be overlooked. Sepsis per se is manifested by repeated rigors

TABLE 13. BACTERIOLOGY OF POSTANGINAL SEPTICEMIA

- *Fusobacterium necrophorum* is key pathogen
- *Fusobacterium prausnitzii*
- *Fusobacterium nucleatum*
- *Fusobacterium gonidiaformans*
- *Bacteroides fragilis*
- Other *Bacteroides*
- *Peptostreptococcus*

and high fevers and, at times, a stiff neck[178] and jaundice.[179] There is a surprisingly high frequency of metastatic infection, which is chiefly a result of septic embolization. Metastatic foci of infection may be seen essentially anywhere in the body, but septic emboli to the lungs and pleural space and septic arthritis and osteomyelitis are especially common. Other sites of infection include the central nervous system (brain abscess, meningitis), the liver, the pericardium, and soft tissue.

The disease is seen primarily in children but also is seen in young adults and, on occasion, in older individuals. The disease was much more common in the preantimicrobial era but occurs with surprising frequency still — considering that the causative organisms are typically very sensitive to many antimicrobial agents commonly used for tonsillopharyngitis. In this connection, however, it should be noted that the primary organism in this process is *F necrophorum* and sometimes other fusobacteria and that these organisms are typically resistant to erythromycin.[35] Erythromycin may be used as an alternative to penicillin for tonsillopharyngitis, and there are descriptions of failures of response in patients so treated.[177,178] The primary pathogens in postanginal sepsis are anaerobes, with, as noted, *F necrophorum* far and away the most commonly encountered. Table 13 lists other species of *Fusobacterium* that have been encountered, as well as other anaerobes. On occasion, nonanaerobic organisms may be the cause of this clinical entity; included are group A and α-hemolytic streptococci, pneumococci, *S aureus, Eikenella corrodens*, and *Hemophilus influenzae*.

Prior to the availability of antimicrobial agents, oropharyngeal infection was by far the most common background for anaerobic septicemia. This is no longer the case, since antimicrobial agents have become available, but as noted above, this very serious illness occurs with surprising frequency, as indicated by numerous reports in the literature.[5,177-181]

In terms of diagnostic approaches to postanginal septicemia, those outlined above for jugular thrombophlebitis would be part of the approach. In addition, one should perform anaerobic and aerobic blood cultures and gallium or indium scans; ultrasound and axial CT may be useful for detection of metastatic abscesses. Finally, abscess contents should be cultured.

The therapeutic approach to postanginal septicemia is outlined in Table 14. Obviously, if an organism other than *Fusobacterium, Peptostreptococcus*, or penicillin G–susceptible *Bacteroides* is isolated, another therapeutic approach will be required. Metronidazole would be suitable for β-lactamase–producing *Bacteroides*, including members of the *B fragilis* group. Antimicrobial therapy should be given for a minimum of 6 weeks in order to prevent relapse. Therapy would need to be individualized in the case of the occasional patient who has infection due to a nonanaerobic organism.

TABLE 14. THERAPY OF POSTANGINAL SEPTICEMIA

- Antimicrobial therapy (prolonged)
  - Penicillin G (or metronidazole)
  - Erythromycin *not* effective
- Surgical or percutaneous drainage of focal infection
- Ligation or surgical excision of infected vein may be required
- Anticoagulation helpful in some cases; possibly risky

TABLE 15. CLINICAL FEATURES OF PERITONSILLAR ABSCESS (QUINSY)

- Cardinal features
  - Preceding tonsillitis
  - Dysphagia, trismus, dysarthria, drooling
  - Localized pharyngeal swelling; soft palate displaced medially; uvula to opposite side
  - Anterior cervical adenitis
- "Hot potato" voice due to edema of soft palate and uvula and pain
- May have necrotic tonsillar ulceration, exudate

*Peritonsillar Abscess and Cellulitis.* Complications of anaerobic tonsillitis involving local extension include peritonsillar abscess or cellulitis and various neck space infections. This section will deal with peritonsillar abscess and cellulitis, and subsequent sections will deal with various neck space infections.

Peritonsillar abscess (quinsy) is the most common deep infection of the head and neck. It is not a true neck space infection. Infection does extend beyond the capsule of the tonsil, but is limited by fascia of the middle constrictor muscle. Peritonsillar abscess is a disease of adolescents and adults. It is rare in children under the age of 12. It is interesting to speculate on the possibility that this pattern may be related to changes in oral microflora that occur with age. The frequency of isolation of black-pigmented *Bacteroides* and spirochetes increases by age 13 to 16 as compared with the prepubertal period.[183]

The distinctive clinical features of peritonsillar abscess are noted in Table 15. It should be appreciated that peritonsillitis is a continuum, ranging from cellulitis to abscess. Peritonsillar abscess is significantly more frequent in the older pediatric patient, ie, the adolescent, whereas peritonsillar cellulitis is more common in younger patients.[184] Again, this may be related to differences in oral microflora. There are a number of bacteriologic studies of peritonsillar abscess in the literature. Summaries of these studies are provided by Baker and Montgomery[185] and Finegold.[35] Individual studies are presented in papers by Brook,[52,186] Flodstrom and Hallander,[187] and Stegehuis and Schousboe.[188] The bacteriology of peritonsillar abscess is summarized in Table 16.

In the preantimicrobial era, complications of peritonsillar abscess were common and feared. Stegehuis and Schousboe[188] cite an earlier study of 34 deaths from hemorrhage associated with peritonsillar abscess in a 1933 paper and a report in 1875 of 226 people in England who died with the diagnosis of quinsy. Infection may spread to the parapharyngeal space (discussed below) and proceed to cause erosion of the carotid artery, mediastinitis, or intracranial complications. There may be obstruction of the airway or spontaneous rupture of the abscess with aspiration leading to lung abscess. Remote complications include peritonitis, nephritis, and endocarditis. All of these are rare in the antimicrobial era. Computed tomography of the neck

TABLE 16. BACTERIOLOGY OF PERITONSILLAR ABSCESS

- Anaerobes
  - Pigmented *Bacteroides*
  - *Bacteroides fragilis* group
  - Other *Bacteroides*
  - *Fusobacterium necrophorum*
  - *Fusobacterium nucleatum*
  - Other *Fusobacterium*
  - *Peptostreptococcus*
  - *Veillonella*
  - *Bifidobacterium*
  - *Eubacterium*
  - *Clostridium*
  - *Actinomyces*, *Arachnia*
- Nonanaerobes
  - β-Hemolytic *Streptococcus*, group A
  - β-Hemolytic *Streptococcus*, non-group A
  - Viridans streptococci
  - γ-Hemolytic streptococci
  - *Hemophilus influenzae*
  - Other *Hemophilus*
  - *Staphylococcus aureus*
  - *Staphylococcus epidermidis*
  - *Eikenella corrodens*

TABLE 17. THERAPY OF PERITONSILLAR ABSCESS

- Antimicrobial therapy
  - Metronidazole plus penicillin or β-lactam agent plus β-lactamase inhibitor
- Drainage
  - Needle aspiration
  - Incision and drainage, if necessary
- Tonsillectomy, if indicated

may be helpful in defining complications of peritonsillar abscess and, on occasion, may define a peritonsillar abscess that is not clearly evident on physical examination.

Therapy of peritonsillar abscess is outlined in Table 17. In addition to antimicrobial therapy, drainage is important; it is usually possible to drain effectively by needle aspiration, but surgical drainage may be necessary. Antimicrobial agents should be given for at least 2 to 3 weeks. Tonsillectomy may be performed eventually if there is a history of recurrent tonsillitis or previous peritonsillar abscess.

*Parapharyngeal Abscess.* Neck space infections will be discussed elsewhere in this symposium, so they will be mentioned only briefly here in relation to the tonsil.

Peritonsillar abscess frequently spreads by a lateral pathway to the parapharyngeal space. The tonsillitis may appear to subside completely before the parapharyngeal space infection manifests itself. In fact, the interval between the two may be as long as several weeks; accordingly, the history of a preceding sore throat or respiratory infection is very important. The triad of signs indicating a parapharyngeal abscess includes 1) prolapse of the tonsillar fossae and swelling of the lateral pharyngeal wall, 2) trismus, and 3) parotid region swelling. Whereas in uncomplicated peritonsillar abscess the fever is usually not high and sepsis not severe (the key features are the extreme misery of the patient and local discomfort), in parapharyngeal space infection the patient has a high fever with chills and sweats. Complications of parapharyngeal space infections include 1) infection of the carotid sheath, which may lead to erosion of the internal carotid artery and fatal hemorrhage, 2) thrombophlebitis of the internal jugular vein with intracranial extension, 3) necrotizing fasciitis, 4) upper airway obstruction, 5) mediastinitis, and 6) septicemia.

Computed tomography is helpful in evaluating the site and extent of infection. External drainage is mandatory, along with antimicrobial therapy.

*Retropharyngeal Abscess.* Infection of the retropharyngeal space is usually an extension from parapharyngeal space infection, or it may result from lymphatic drainage from the nasopharynx or other sites. The classic signs and symptoms include dysphagia, hoarseness, drooling, swelling of the posterior pharyngeal wall, and meningismus. This space infection may be complicated by mediastinitis or rupture into the pharynx with aspiration and subsequent pneumonia and empyema. Jugular vein thrombosis and hemorrhage from one of the larger vessels in the neck are other complications. A summary of reported cases relating to tonsillitis or pharyngitis is provided by Finegold.[35]

*Other Neck Space Infections.* The importance of preceding tonsillitis or tonsillopharyngitis in neck space infections in general is emphasized by the series reported by Brook[189] and Tom and Rice.[190] Information as to the specific neck space infections related to tonsillar or tonsillopharyngeal infection is not provided, but it is interesting to note that roughly 10% of abscesses of the neck were related to preceding tonsillitis or tonsillopharyngitis. Finally, Liebshardt et al[191] report a case of necrotizing gas-forming infection of the neck secondary to a tonsillar abscess. Culture yielded *Bacteroides* and *Peptostreptococcus*, as well as *Propionibacterium acnes*. The case is described as nonclostridial gas gangrene, but probably represents anaerobic cellulitis or necrotizing fasciitis.

# ROLE OF ANAEROBIC BACTERIA IN PERIMANDIBULAR SPACE INFECTIONS

JANET HORN, MD; BRADLEY S. BENDER, MD; JOHN G. BARTLETT, MD

## INTRODUCTION

Space infections of the head and neck generally arise from extensions of bacterial infections of the upper airways to involve the potential spaces formed by fascial planes. These conditions were once relatively common and were the subject of classic descriptions in the prepenicillin era.[192-198] However, they have become sufficiently rare during the antibiotic era so that they are poorly understood, often mismanaged, and infrequently reviewed.[185,199] The purpose of this report is to review space infections that occur adjacent to the mandible by including pathophysiology, anatomy, bacteriology, and management. The initial section will deal with background information, with special emphasis on the anatomy of perimandibular space infections, and the second section is a review of the experience with these infections at Johns Hopkins Hospital for the 5-year period from January 1, 1979, through December 31, 1983.

## BACKGROUND

*Anatomy and Associated Conditions.* The potential spaces formed by fascial insertions along the mandible are contiguous, so that multiple spaces may be involved. Nevertheless, most of these infections remain relatively confined to specific anatomic sites that reflect a specific portal of entry that, in turn, dictates the predominant bacterial pathogens (Table 18). In general, there are two major portals of entry: the posterior pharynx, in which group A β-hemolytic *Streptococcus* represents a particularly important pathogen, and dental infections, in which anaerobic bacteria appear to be the predominant pathogens.

Space infections associated with pharyngeal infections may be peritonsillar, retropharyngeal, or parapharyngeal. In most instances, these infections represent a complication of an upper respiratory tract infection such as pharyngitis or tonsillitis, although the initiating focus of infection may have resolved by the time the deeper structures become involved. Peritonsillar abscess (quinsy) represents a suppurative infection that has extended beyond the capsule of the tonsil, but is limited by the fascia of the middle constrictor muscle. This is not a true space infection, since it does not involve the contents of a fascial plane. Most cases occur in older children, and the usual findings are a preceding throat infection, dysphagia, swelling in the tonsillar pillar, and cervical adenitis. The traditional pathogen involved in peritonsillar abscess infections is group A β-hemolytic *Streptococcus*. However, studies by Flodstrom and Hallander[187] indicate that anaerobic bacteria, especially *Peptostreptococcus*, are actually more prevalent in these infections.

Parapharyngeal space (lateral pharyngeal space) infections are particularly important to recognize because of potential complications. This space represents an inverted cone with the base at the sphenoid bone and the apex at the hyoid bone. The styloid process protrudes into the space and divides it functionally into the anterior compartment and the posterior compartment. The posterior compartment contains the carotid sheath with the carotid artery and the jugular vein. Posteriorly, this space communicates with the retropharyngeal space. Infections in the parapharyngeal space may arise from adjacent structures in the pharynx or represent extension from other contiguous spaces, so that the initial portal of entry may be the pharynx, teeth, tonsils, adjacent lymph nodes draining the nose and pharynx, and contiguous spaces including the submandibular space, retropharyngeal space, and masticator space. Clinical features of infections involving the anterior compartment include trismus, induration and swelling at the angle of the mandible, systemic toxicity with high fever and constitutional symptoms, and swelling of the pharyngeal wall on physical examination. Infections involving the posterior compartment may be complicated by suppurative thrombosis of the jugular vein, which is commonly associated with *Fusobacterium necrophorum* bacteremia, metastatic abscesses to the lung, and severe sepsis with chills and, on occasion, hypotension. This constellation of findings was classically described by Lemierre[197] in 1936, and the condition has come to be referred to as Lemierre's syndrome and has been subject to at least three recent reviews.[177,200,201]

TABLE 18. FASCIAL SPACES OF HEAD AND NECK

| *Location* | *Space* | *Common Portal of Entry* | *Predominant Bacteria* |
|---|---|---|---|
| Posterior pharynx | Peritonsillar | Pharynx | *Streptococcus pyogenes* or anaerobes |
| | Parapharyngeal | Pharynx, mastoid, lower molars, extension from other spaces | *Streptococcus pyogenes* or anaerobes |
| | Retropharyngeal | Pharynx | *Streptococcus pyogenes* |
| Upper jaw | Canine | Dental: anterior upper teeth and biscuspids | Anaerobes |
| Mandible | Submental | Dental: lower second and third molars | Anaerobes |
| | Buccal | Dental: lower first and second molars | Anaerobes |
| | Sublingual | Dental: lower bicuspids | Anaerobes |
| | Masticator | Dental: third molars | Anaerobes |
| | Mandibular | Dental: bicuspids, first and second molars | Anaerobes |
| | Parotid | Stensen's duct | *Staphylococcus aureus* or anaerobes |
| Neck | Superficial | Skin | *Staphylococcus aureus* |
| | Visceral | Pharyngeal, tracheal, esophageal, or laryngeal trauma | Anaerobes |
| | Carotid sheath | Extension from parapharyngeal space | Anaerobes or *Streptococcus pyogenes* |
| | Prevertebral | Vertebral osteomyelitis | *Staphylococcus aureus* |
| | Danger space | Extension from visceral or prevertebral spaces | *Staphylococcus aureus* |

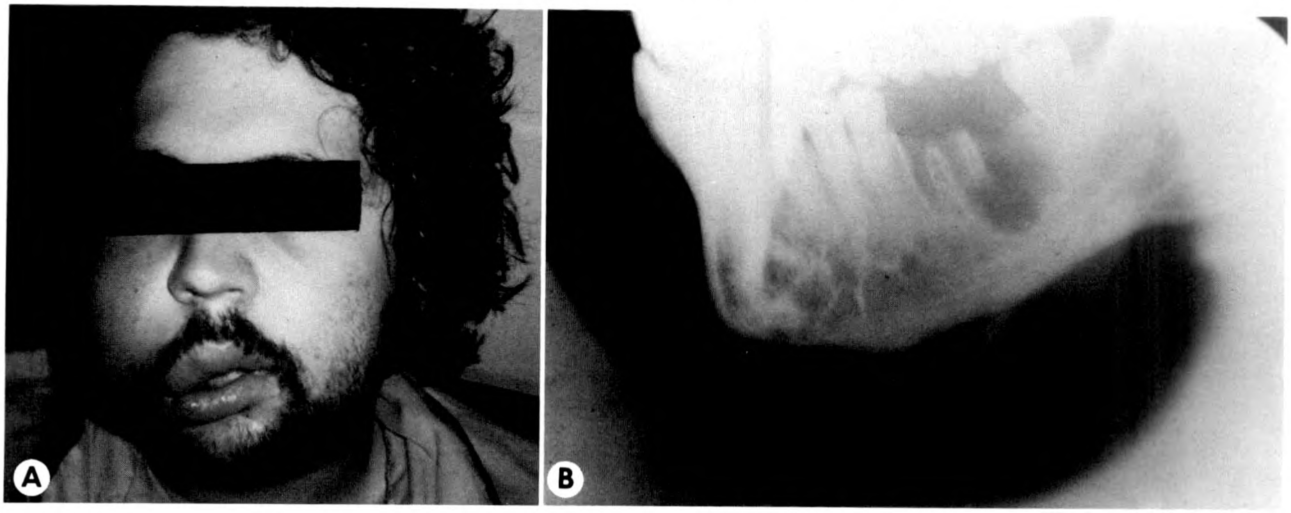


Fig 12. A) Submandibular space infection. Notice mandibular swelling indicative of most common space infection portal of entry: molar tooth. B) Periapical abscess at site of extracted molar tooth associated with lesion in A.

Space infections that occur more anterior along the mandible usually represent complications of dental procedures or untreated suppurative pulpitis. A common sequence is an endodontal infection that extends to the periapical space with a periapical abscess that, if unattended, may penetrate through the mandible to involve the potential spaces created by fascial insertions. Although these spaces are contiguous, there does tend to be localized involvement reflecting specific teeth as the portal of entry. Most common are the space infections associated with a molar tooth portal of entry, since the mandibular plate is relatively thin at this site. The usual bacteria found in these cases are anaerobic bacteria, which represent the dominant pathogens in endodontal infections, periapical abscess, and periodontal infections.[202-205] Patients with more anterior perimandibular space infections generally present with localized swellings that occur along the mandible (Figs 12 and 13). These swellings are tender and are usually associated with fever, and common preceding events include a dental procedure, neglected dental problems, or trauma.

A particularly important type of infection included in the perimandibular space infections occurring along the anterior mandible is Ludwig's angina. This was originally described in 1836 in one of the two publications of von Ludwig as a "gangrenous induration of connective tissue of the neck which advances to involve the tissues that cover the small muscles between the larynx and the floor of the mouth."[206] Diagnostic criteria include bilateral involvement of both the sublingual and submandibular spaces. The typical presentation is an indurated swelling of the submandibular region reflecting involvement of the submandibular space and elevation of the tongue reflecting infection of the sublingual space. The latter finding is responsible for dyspnea, which accounts for the term angina. Drainage of these lesions commonly yields thin, greyish, and putrid fluid ("dishwater pus") that is similar to the discharge noted in necrotizing synergistic cellulitis, a devastating mixed aerobic-anaerobic infection of soft tissue.[207]

*Clinical Presentation*. Patients with premandibular space infections generally present with localized swelling along the mandible that reflects the anatomic site of infection (Figs 12-14). These swellings are tender and are associated with fever. Common associated conditions include preceding dental procedures, neglected dental problems, oral trauma, or pharyngeal infection. Trismus indicates irritation involving the muscles of mastication, primarily the masseter and internal pterygoid muscles. Most frequently this is found with infections of the anterior compartment of the parapharyngeal space or the masticator space. Dysphagia is most frequently found with infections adjacent to the pharynx, including the parapharyngeal and retropharyngeal spaces. Dyspnea is noted with involvement of the sublingual and/or submandibular spaces (Ludwig's angina), the posterior compartment of the parapharyngeal space, or the retropharyngeal space.

The differential diagnosis of these tender swellings along the mandible should include three conditions that are different in terms of the bacteria involved and management guidelines. These include actinomycosis, suppurative parotitis, and suppurative adenitis. Actinomycosis typically causes a highly characteristic woody induration along the mandible and is often accompanied by a draining sinus, but it may also present as a fluctuant mass that simulates a perimandibular space infection. Actinomycosis does not represent a space infection, because this condition does not respect anatomic boundaries. Suppurative parotitis is usually a condition of elderly or dehydrated patients, and the

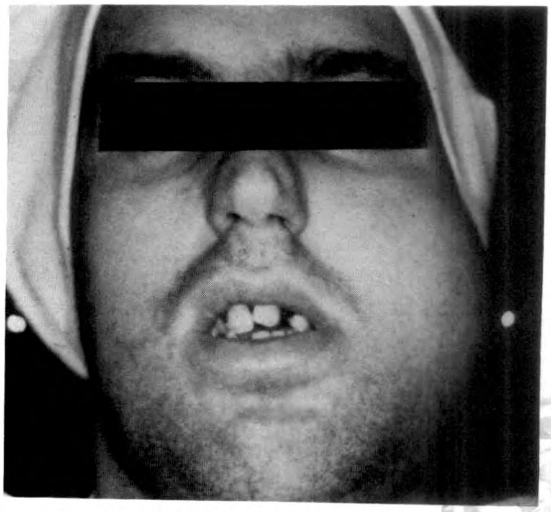


Fig 13. Masticator space infection.

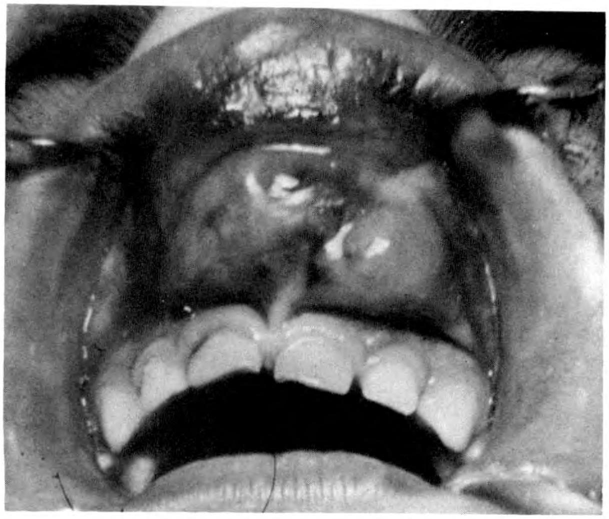


Fig 14. Vestibular space infection.

most frequent bacterial pathogen is *Staphylococcus aureus*, although anaerobic bacteria have occasionally been implicated.[208] Lymph nodes of the cervical region include 10 major groups, 6 of which are located at the junction of the head and neck.[185] Those located along the mandible, and consequently most problematic in the differential diagnosis of space infections, include the carotid, submaxillary, and submental lymph nodes. Swelling of the carotid lymph nodes may simulate suppurative parotitis or mumps. Submandibular lymph nodes receive lymph drainage from the lower teeth, floor of the mouth, and tongue. The deep lateral cervical chains receive drainage from all of the lymphatics of the head and neck and are located adjacent to the carotid sheath, posing the potential for direct invasion with bacteremia.

The diagnosis of perimandibular space infections, as well as space infections in adjacent areas, is often facilitated with computed tomography (Fig 15). This especially applies to potentially serious space infections including parapharyngeal space infections, Ludwig's angina, and posterior space infections including the vertebral space, the retropharyngeal space, and the "danger space."

TABLE 19. BACTERIOLOGY OF PERIMANDIBULAR SPACE INFECTIONS*

| | *Chow et al*[209] *(31 Cases)* | | *Bartlett and O'Keefe*[210] *(21 Cases)* | |
|---|---|---|---|---|
| | *No.* | *%* | *No.* | *%* |
| Aerobes only | 1 | 3 | 0 | |
| Anaerobes only | 13 | 42 | 1 | 5 |
| Aerobes and anaerobes | 16 | 52 | 20 | 95 |
| Mean isolates per specimen | 4 | | 5.2 | |
| Predominant isolates | | | | |
| Aerobes | | | | |
| *Streptococcus* | 14 | 11 | 20 | 18 |
| *Staphylococcus aureus* | — | — | 3 | 3 |
| Miscellaneous | — | — | 9 | 8 |
| Anaerobes | | | | |
| *Peptostreptococcus*† | 23 | 19 | 25 | 22 |
| *Fusobacterium* | 7 | 6 | 7 | 6 |
| *Bacteroides melaninogenicus*§ | 15 | 12 | 9 | 8 |
| *Bacteroides* sp (other) | 6 | 5 | 9 | 8 |
| *Veillonella* sp | 3 | 2 | 3 | 3 |
| *Actinomyces* | 4 | 3 | 4 | 4 |
| Nonsporulating gram-positive bacteria (other) | 7 | 6 | 21 | 19 |

Percentages refer to percentage of total species recovered.

*Johns Hopkins Hospital, 1979-1983.

†Organisms previously classified in genera *Peptococcus* have been reclassified into genera *Peptostreptococcus*, except for *Peptococcus niger*. Some organisms previously classified as *Peptostreptococcus* are now reclassified as aerobic or microaerophilic streptococci, including *Streptococcus intermedius*, *Streptococcus parvulus*, *Streptococcus constellatus*, and *Streptococcus morbilorum*.

§Organisms previously classified as *Bacteroides melaninogenicus* are now reclassified into two genera and 10 species, with predominant species in orodental infections being *Bacteroides intermedius* and *B melaninogenicus*.

*Bacteriology*. There were extensive studies of the bacteriology of perimandibular space infections in the preantibiotic era that called appropriate attention to the important role of anaerobic bacteria in most cases. More recently, most of the literature concerns single case reports, particularly for specific types of infections such as Lemierre's syndrome with bacteremia, in which *F necrophorum* is clearly the dominant pathogen.[177,200,201] There are two relatively large series dealing with bacteriologic studies of exudate in patients with perimandibular space infections. One is by Chow et al,[209] dealing with 14 perimandibular space infections and 13 cases of mandibular osteomyelitis. A second report is from our group, dealing simply with bacteriologic studies of exudate in patients with perimandibular space infections.[210] The findings in these two studies are summarized in Table 19.[209,210] The predominant isolates are anaerobic bacteria, although aerobic and microaerophilic streptococci are commonly found as well. Most infections are polymicrobial, with the predominant anaerobic bacteria being anaerobic streptococci (*Peptostreptococcus*), *Fusobacterium* species (especially *F nucleatum*), and black-pigmenting strains of *Bacteroides*, previously referred to as *Bacteroides melaninogenicus*. As expected, these are the same organisms that are encountered in the normal flora of the gingival crevice, and are also dominant pathogens in endodontal infections, periapical infections, aspiration pneumonia, and lung abscess. Relevant taxonomic changes that have taken place since these studies were published[209,210] include deletion of the genera *Peptococcus* except for *Peptococcus niger*, the reassignment of several species of *Peptostreptococcus* to facultative or microaerophilic *Streptococcus* species, and the reassignment of *B melaninogenicus* into two genera with at least 10 species.

The other two bacterial pathogens that appear important in these types of infections include group A β-hemolytic *Streptococcus* and *S aureus*. Both of these organisms tend to be associated with specific portals of entry and specific types of space infections. With group A β-hemolytic streptococcal infection, as expected, the usual portal of entry is the posterior pharynx, with involvement of spaces adjacent to that region including peritonsillar abscess, occasional parapharyngeal infections, and retropharyngeal infections. *Staphylococcus aureus* represents the most common cause of suppurative parotitis and prevertebral space infections that usually occur in association with vertebral osteomyelitis, and the "danger space" represents an extension of infections involving the prevertebral space. *Actinomyces* species may be involved in polymicrobial infections, but actinomycosis is a characteristic infection that is distinctive, as noted above (Fig 16).

*Treatment and Outcome*. The mainstays of treatment

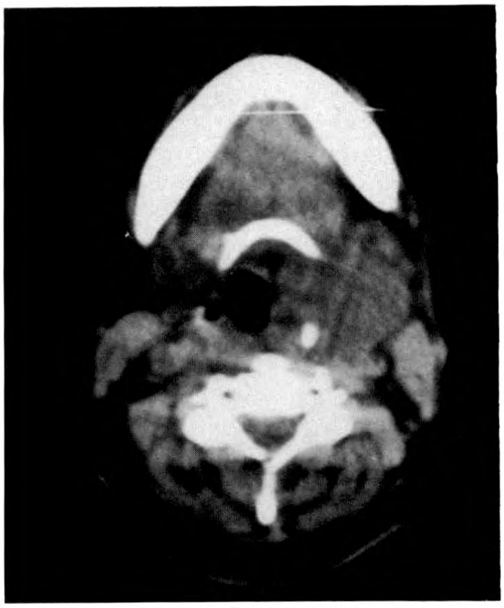


Fig 15. Computed tomography scan showing displacement of airway by parapharyngeal space infection. This patient also had *Fusobacterium bacteremia* and septic emboli to lung, ie, Lemierre's syndrome.

for perimandibular space infections include drainage, antibiotics, and, in the event of a dental portal of entry, dental care.

The selection of antibiotics is obviously facilitated by accurate definition of bacteriology. This requires the use of meticulous cultures for anaerobic bacteria, including the use of specimens that are uncontaminated by the normal flora of the upper airways. Accurate bacteriology results may be difficult to achieve, especially early in the infection when therapeutic decisions are often required. Fortunately, the bacteriology patterns are quite predictable in that the majority involve multiple anaerobic bacterial species, often combined with aerobic and microaerophilic streptococci. On the basis of this observation, empiric selection of antibiotics often includes penicillins, clindamycin, or metronidazole. When metronidazole is used, it is prudent to add penicillin in view of the potentially important role of microaerophilic and aerobic streptococci in mixed infections.

There are three types of infections that are associated with relatively severe and sometimes life-threatening complications. These include chest infections, vascular complications, and airway obstruction.

Chest infections include mediastinitis, pericarditis, aspiration pneumonia, and septic emboli to the lung. Direct extension to the mediastinum as a complication of infections of the head and neck usually reflects involvement of the retropharyngeal, prevertebral, and/or danger spaces that are located between the spine and the esophagus or pharynx. The most common route via the neck is the danger space; this fact accounts for its name.

Vascular complications include infection of the carotid sheath with rupture of the carotid artery or suppurative thrombophlebitis of the internal jugular vein and/or bacteremia. The most frequently recognized complication in recent years has been Lemierre's syndrome in association with infection of the posterior compartment of the parapharyngeal space as described above. Infections of the carotid sheath may also be seen as a complication of Ludwig's angina or suppurative lymphadenitis involving the deep cervical nodes complicating pharyngeal, tonsillar, or submandibular infections.

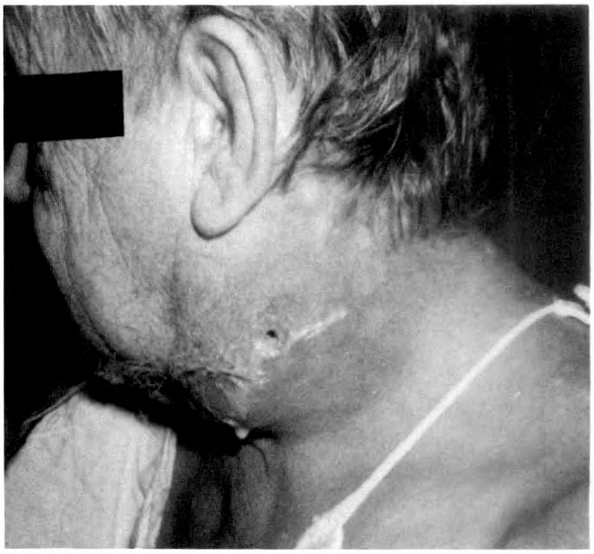


Fig 16. Actinomycosis with draining sinus.

The most frequent severe complication of Ludwig's angina is airway obstruction; this fact accounts for maintenance of the airway as the most compelling immediate therapeutic aim. Other potential complications include aspiration pneumonia, necrosis of the tongue, and extension to the parapharyngeal or retropharyngeal space.

## RETROSPECTIVE STUDY

*Methods*. The purpose of this study was to describe the clinical features of perimandibular space infections as they are encountered in a large teaching hospital. The study involved all patients hospitalized at the Johns Hopkins Hospital during the period January 1, 1979, through December 31, 1983. Cases were identified by record review for a diagnosis of a perimandibular space infection among patients hospitalized during the period of review. Identification of spaces involved was based on the interpretation of the otolaryngologist or oral surgeon, or by chart and x-ray review. The review was limited to patients 18 years or older.

*Patient Characteristics*. There were 44 patients who fulfilled entry criteria, including 23 men and 21 women (Table 20). Most were relatively young, including 36 (82%) between the ages of 18 years and 40 years.

Patients admitted for this diagnosis presented to the emergency room, otolaryngology clinic, or dental clinic, the most common of the three being the emergency room, which accounted for 43%. There were eight (18%) patients admitted for an alternative diagnosis who had a perimandibular space infection either at the time of admission or during their course of hospitalization. All patients were hospitalized, but the service location varied among the otolaryngology, oral surgery, and medical services.

Most patients had a relatively brief duration of symptoms prior to admission, ie, 1 to 3 days for 20 patients (46%), 4 to 7 days for 15 (34%), and longer than 7 days for 8 (18%). There were 14 patients (32%) who had received

TABLE 20. PERIMANDIBULAR SPACE INFECTIONS: PATIENT CHARACTERISTICS*

| | |
|---|---|
| Sex | |
| Male | 23 |
| Female | 21 |
| Age | |
| 18 to 30 years | 25 (57%) |
| 31 to 40 years | 11 (25%) |
| 41 to 50 years | 3 ( 7%) |
| Over 50 years | 5 (11%) |
| Presented to | |
| Emergency room | 19 (43%) |
| Otolaryngology clinic | 6 (14%) |
| Dental clinic | 11 (25%) |
| Admitted for alternative diagnosis | 8 (18%) |
| Duration of symptoms prior to presentation | |
| 1 to 3 days | 20 (46%) |
| 4 to 7 days | 15 (34%) |
| 8 to 21 days | 5 (11%) |
| Over 21 days | 3 ( 7%) |
| Recent dental extraction | 10 (23%) |
| Prior therapy | 14 (32%) |
| Antibiotics only | 10 |
| Incision and drainage only | 1 |
| Both | 3 |
| Clinical features | |
| Facial swelling | 37 (84%) |
| Admission temperature exceeding 37.7°C | 30 (68%) |
| Tender cervical adenopathy | 14 (32%) |
| Peripheral leukocyte count exceeding 10,000/mm$^3$ | 37 (84%) |
| Associated medical conditions† | 18 (41%) |

*Johns Hopkins Hospital, 1979-1983.

†Include alcoholism (11 patients), intravenous drug abuse (4), diabetes mellitus (4), chronic corticosteroid use (2), chronic renal failure (1), congenital heart disease (1), pregnancy (1), and recurrent tonsillitis (1).

previous therapy, including 4 who had undergone previous incision and drainage for the current infection. An additional 10 patients (23%) had a recent dental extraction and 18 (41%) had associated medical conditions, the most common being alcoholism, intravenous drug use, and diabetes mellitus (Table 20).

*Clinical Findings.* Facial swelling was noted in 37 (84%), 30 patients (68%) had an admission temperature exceeding 37.7°C, "poor dental hygiene" was noted in 15 (34%), and lymphadenopathy was recorded for 14 (32%). Admission laboratory studies showed a leukocytosis with peripheral leukocyte counts exceeding 10,000/mm$^3$ in 37 (84%), and it was over 20,000/mm$^3$ in 5 (11%).

*Spaces Involved.* There were 29 (66%) patients with a single space involved and 15 (34%) who appeared to have multiple spaces. The most frequent sites were the submandibular space, peritonsillar space, parapharyngeal space, buccal space, and sublingual space (Table 21). Two patients had Ludwig's angina and 2 had parapharyngeal space infections associated with *Fusobacterium* bacteremia with metastatic abscesses to the lungs. Correlation with the site of involvement and associated conditions followed predictable patterns (Table 22). All patients with peritonsillar abscesses had a history suggesting pharyngitis. There were 18 (41%) patients with a dental portal of entry, the most common spaces being the submandibular and buccal spaces. There were 4 (9%) patients whose infection appeared to be associated with trauma, and 8 (18%) in whom no likely portal of entry was identified.

TABLE 21. PERIMANDIBULAR SPACE INFECTIONS: SPACES INVOLVED*

| | *Total (44 Patients)* | | *Single Space† (29 Patients)* | |
|---|---|---|---|---|
| | *No.* | *%* | *No.* | *%* |
| Submandibular§ | 16 | 36 | 8 | 28 |
| Peritonsillar | 14 | 32 | 8 | 28 |
| Parapharyngeal | 10 | 23 | 5 | 17 |
| Buccal | 8 | 18 | 6 | 21 |
| Sublingual§ | 6 | 14 | 0 | |
| Canine | 1 | 2 | 1 | 3 |
| Masticator | 1 | 2 | 1 | 3 |

*Johns Hopkins Hospital, 1979-1983.

†Refers to patients believed to have only one space involved.

§Two patients had Ludwig's angina.

*Treatment and Course.* All patients received antimicrobial agents, the most common being penicillin G for 35 patients, other $\beta$-lactams for 11, and clindamycin for 9 (Table 23). Surgical procedures were performed in 39 of the 44 patients. In most cases, this was a drainage procedure or tooth extraction; 5 patients underwent a tonsillectomy, including 2 with a peritonsillar abscess, 2 with parapharyngeal space infections, and 1 with both.

*Outcome.* All patients were cured of their infection, although 8 had serious complications. The most frequent complication was airway obstruction requiring tracheostomy in 6. The 2 additional patients had Lemierre's syndrome with the characteristic features of bacteremia and septic emboli to the lung (Table 23). Most of the patients had a brief hospital course — 3 days or less for 17 (39%) and 7 days or less for 26 (60%). There were 10 patients (23%) who were hospitalized for more than 14 days, including 7 with parapharyngeal space infections.

## DISCUSSION

Space infections of the head and neck were relatively common complications of dental and pharyngeal infections in the preantibiotic era. During the last 40 years, there has been a substantial decline in the frequency of these infections, so that they are relatively obscure to most practitioners. We are not aware of recent publications in the form of an original series; this lack prompted this review.

Results of our review indicate that four medical specialties participate in the care of these patients, including medicine, oral surgery, otolaryngologic surgery, and dentistry. It was noted in the review that there appeared to be a particular problem in recognizing the anatomy, physiology, and bacteriology of this infection by primary care physicians, possibly due to the fact that the usual com-

TABLE 22. PERIMANDIBULAR SPACE INFECTIONS: UNDERLYING CONDITIONS*

| *Space* | *Odontogenic (18 Pts or 41%)* | *Pharyngitis (14 Pts or 32%)* | *Trauma (4 Pts or 9%)* |
|---|---|---|---|
| Peritonsillar | 0 | 14 | 0 |
| Submandibular | 11 | 1 | 2 |
| Parapharyngeal | 2 | 6 | 1 |
| Buccal | 6 | 0 | 2 |
| Sublingual | 3 | 0 | 0 |
| Masticator | 2 | 0 | 0 |

*Johns Hopkins Hospital, 1979-1983.

TABLE 23. PERIMANDIBULAR SPACE INFECTIONS: TREATMENT AND COURSE*

| | |
|---|---|
| Surgical procedure | 39 |
| Drainage | 30 |
| Tooth extraction | 17 |
| Tonsillectomy† | 5 |
| Antimicrobial agents | |
| Penicillin | 35 |
| Clindamycin | 9 |
| Other§ | 19 |
| Complications | |
| Airway obstruction requiring tracheostomy | 6 |
| Bacteremia | 2 |
| Septic emboli | 2 |
| Sinus tract or fistula | 1 |
| Duration of hospitalization | |
| 1 to 3 days | 17 (39%) |
| 4 to 7 days | 9 (21%) |
| 8 to 14 days | 8 (18%) |
| Over 14 days∮ | 10 (23%) |

*Johns Hopkins Hospital, 1979-1983.

†Includes two patients with peritonsillar abscess, two with lateral pharyngeal abscess, and one patient with both.

§Includes nafcillin (5 patients), aminoglycoside (5), ampicillin (3), chloramphenicol (2), metronidazole (1), cefoxitin (1), cefamandole (1), and cephalothin (1).

∮Includes seven patients with lateral pharyngeal space infection.

plaints are similar to those of many other common types of infections. Further, there appeared to be confusion regarding referral patterns, since oral surgery, otolaryngologic surgery, and dentistry all represent disciplines with overlapping prerogatives. These points are important to emphasize, since potential complications include bacteremia, metastatic abscesses, extension of infection to the mediastinum, and airway compromise. Early recognition and prompt institution of appropriate treatment is important to prevent these complications or to manage them once they have taken place.

Despite potential confusion, these infections are relatively straightforward in terms of pathophysiology, bacteriology, and management guidelines. The majority of these infections represent complications of dental infections or pharyngitis in young, otherwise healthy adults. The bacteriology patterns are quite predictable, with group A β-hemolytic streptococci representing important potential pathogens for those infections in which the posterior pharynx or tonsillitis represents the portal of entry. Anaerobic bacteria are the predominant pathogens when there is a dental portal of entry, although anaerobes may also be associated with what appears to be a pharyngeal portal of entry. These include the same anaerobic species that are found in the gingival crevice, endodontal infections, periapical abscess, and anaerobic pleural pulmonary infections. *Staphylococcus aureus* is commonly suspected, but it is relatively rare except in specific forms of infection such as parotitis or in prevertebral space infections.

Management guidelines are variable, depending on the space or spaces involved. The most important principles are drainage, antimicrobial therapy directed against the likely or established pathogen, and preservation of the airways. Computed tomography represents a notable advance in the diagnostic evaluation for patients with potential complications.

## SUMMARY

This review includes 44 patients with perimandibular space infections admitted to Johns Hopkins Hospital during a 5-year period. The most frequent spaces involved were the submandibular, peritonsillar, and parapharyngeal spaces. As expected, 1) peritonsillar abscesses were invariably associated with pharyngitis, 2) submandibular and buccal space infections generally represented complications of dental infections, and 3) parapharyngeal space infections were associated with both portals of entry. Most patients were treated with drainage procedures, and all received antimicrobial agents, the most common being penicillin. Serious complications included potential airway obstruction requiring tracheostomy in six patients with *Fusobacterium* bacteremia and two patients with septic emboli to the lung. All patients survived, and most had a relatively brief hospitalization with no sequelae.

# MICROBIOLOGY AND ANTIBIOTIC RESISTANCE IN ODONTOGENIC INFECTIONS

Sherwood L. Gorbach, MD; William C. Gilmore, DMD; Neilda V. Jacobus, MSc;
H. Chris Doku, DMD; Francis P. Tally, MD

## INTRODUCTION

Odontogenic infections generally involve a mixture of aerobic and anaerobic organisms originating in the oral cavity. The clinical presentations include dentoalveolar infections, periodontal infections, and various infections of the head and neck spaces. Since anaerobic bacteria have the highest concentrations in the normal oral flora, it is hardly surprising that these organisms predominate in these infections as well.[173,210-214]

Several reports have suggested that oral anaerobic bacteria involved in these infections are often resistant to penicillin.[189,215-220] In this study we performed cultures of moderate to severe odontogenic infections and found a much lower incidence of penicillin resistance than that reported by other groups.

## METHODS

This study was performed in parallel with an antibiotic trial[221] comparing the efficacy of penicillin and clindamycin in moderate to severe orofacial infections of odontogenic origin that required drainage and antibiotic therapy based on the judgment of the dentist (W.C.G.). Additional entrance criteria were that the infection had been present for 7 days or less; pus could be obtained upon aspiration; and the patient had no allergies to antibiotics. Patients who had received antibiotics within the previous month were excluded; however, many patients had been started on a regimen of penicillin by the referring doctor, and we allowed up to two doses, or 500 mg, of penicillin to have been taken prior to enrollment provided the other criteria were satisfied.

The aspiration site was isolated with sterile sponges, and the mucosa was decontaminated by a 2-minute scrub with iodophore applicators. The aspirated fluid (0.5 to 3.0 mL) was delivered rapidly to the laboratory for immediate processing.

All specimens were processed in a glove-box anaerobic chamber. Prereduced nonselective and selective media were used. For aerobic and facultative bacteria, blood agar (tryptic soy agar base), chocolate agar, and MacConkey agar were employed. For anaerobes, anaerobic blood agar (brucella agar base), phenyl ethyl alcohol, and laked kanamycin-vancomycin plates were used.

TABLE 24. AEROBIC AND FACULTATIVE BACTERIA IN ODONTOGENIC INFECTIONS

| | *Positive Cultures (n = 41)* | | *Isolates (n = 129)* | |
|---|---|---|---|---|
| | *No.* | *%* | *No.* | *%* |
| Streptococci | | | | |
| α-Hemolytic | 35 | 85 | 65 | 50 |
| β-Hemolytic | 8 | 20 | 9 | 7 |
| γ-Hemolytic | 8 | 20 | 9 | 7 |
| Staphylococci and micrococci | 7 | 17 | 8 | 6 |
| Gram-positive rods | 15 | 37 | 21 | 16 |
| *Neisseria* | 5 | 12 | 6 | 5 |
| Gram-negative rods | 10 | 24 | 11 | 9 |

Antimicrobial susceptibilities or anaerobes were determined by a modified agar dilution technique using a Steer's replicator. The inoculum was adjusted to contain $10^7$ colony-forming units per milliliter. The actual concentration of bacteria per spot was approximately $10^4$ to $10^5$ colony-forming units. Incubation took place in the anaerobic chamber at 37°C for 48 hours. Minimum inhibitory concentrations (MICs) were defined as the lowest concentration of antimicrobial agent that resulted in no growth. A slight haze or one colony was disregarded.[222]

## RESULTS

The study group included 55 patients who met the enrollment criteria. A total of 323 facultative and anaerobic bacteria were isolated from the 55 specimens. There was an average of 6.1 bacterial species per culture, including 3.6 anaerobes and 2.5 facultative organisms. Mixed cultures of facultative and anaerobic bacteria were seen in 41 (74%) patients, anaerobes only in 11 (20%), and facultative organisms only in 3 (6%).

Of the aerobic and facultative bacteria, streptococci were the most common, isolated in over 90% of positive cultures (Table 24). Among the strict anaerobic bacteria, *Bacteroides* species (not *Bacteroides fragilis*) were recovered in 75% of the cultures. The most common species were members of the *Bacteroides melaninogenicus* group, followed by *Bacteroides oris-buccae*. Gram-positive cocci and a variety of gram-negative rods were also isolated with frequency (Table 25).

The overall resistance to penicillin, defined as an MIC equal to or greater than 1.0 mg/mL, was found in 14 (8.9%) of 157 isolates. The resistance rates among *Bacteroides* ranged from 0% in the *B oris-buccae* group to 17% in the other *Bacteroides* species (Table 26). Clindamycin resistance, as defined by an MIC greater than or equal to

TABLE 25. ANAEROBIC BACTERIA IN ODONTOGENIC INFECTIONS

| | *Positive Cultures (n = 48)* | | *Isolates (n = 194)* | |
|---|---|---|---|---|
| | *No.* | *%* | *No.* | *%* |
| *Bacteroides* | 33 | 68 | 59 | 30 |
| *Bacteroides melaninogenicus* (4 species) | 20 | 42 | 25 | 13 |
| *Bacteroides oris-buccae* | 16 | 33 | 18 | 9 |
| Others | 8 | 18 | 16 | 8 |
| *Fusobacterium* | 14 | 29 | 14 | 7 |
| Gram-positive cocci | 38 | 79 | 52 | 27 |
| Gram-positive rods | 34 | 71 | 49 | 25 |
| Nonsporulating | 25 | 52 | 35 | 18 |
| *Actinomyces* | 10 | 21 | 13 | 7 |
| *Clostridium* | 1 | 2 | 1 | 0.05 |

TABLE 26. ANAEROBIC BACTERIA IN ODONTOGENIC INFECTIONS RESISTANT TO PENICILLIN

| | No. | MIC50 (µg/mL) | MIC90 (µg/mL) | Resistant No. | Resistant % |
|---|---|---|---|---|---|
| *Bacteroides melaninogenicus* (4 species) | 19 | <0.125 | 2.0 | 3 | 16 |
| *Bacteroides oris-buccae* | 13 | <0.125 | 0.5 | 0 | |
| *Bacteroides* spp | 12 | 0.25 | 4.0 | 2 | 17 |
| Other gram-negative rods and gram-negative cocci | 21 | 0.25 | 1.0 | 4 | 19 |
| Gram-positive cocci | 49 | <0.125 | 0.25 | 3 | 6 |
| Gram-positive rods | 32 | 0.25 | 0.5 | 2 | 6 |
| *Actinomyces* | 11 | 0.25 | 0.25 | 0 | |
| Total | 157 | | | 14 | 8.9 |

Resistance defined as ≥1.0 µg/mL.

MIC50 — minimal inhibitory concentration of 50% of isolates, MIC90 — minimal inhibitory concentration of 90% of isolates.

TABLE 27. ANAEROBIC BACTERIA IN ODONTOGENIC INFECTIONS RESISTANT TO CLINDAMYCIN

| | No. | MIC50 (µg/mL) | MIC90 (µg/mL) | Resistant No. | Resistant % |
|---|---|---|---|---|---|
| *Bacteroides melaninogenicus* (4 species) | 19 | <0.125 | <0.125 | 0 | |
| *Bacteroides oris-buccae* | 13 | <0.125 | <0.125 | 0 | |
| *Bacteroides* spp | 12 | <0.125 | 0.25 | 0 | |
| Other gram-negative rods and gram-negative cocci | 21 | <0.125 | 1.0 | 2 | 10 |
| Gram-positive cocci | 49 | <0.125 | 0.25 | 1 | 2 |
| Gram-positive rods | 32 | <0.125 | <0.125 | 0 | |
| *Actinomyces* | 11 | 0.25 | 1.0 | 0 | |
| Total | 157 | | | 3 | 1.9 |

Resistance defined as ≥4.0 µg/mL.

MIC50 — minimal inhibitory concentration of 50% of isolates, MIC90 — minimal inhibitory concentration of 90% of isolates.

4.0 µg/mL, was found in 3 (1.9%) of 157 anaerobic isolates (Table 27). None of the 44 *Bacteroides* isolates was resistant to clindamycin.

## DISCUSSION

Moderate to severe orofacial infections of odontogenic origin are generally treated with antibiotics combined with a conventional incision and drainage procedure, followed later by dental extraction or endodontic therapy. While penicillin has been standard treatment for such infections, there is some concern that a high rate of resistance would make this drug an undesirable choice.

Resistance to penicillin among organisms isolated in the oral cavity, particularly *Bacteroides* species, has been reported by several investigators over the past 15 years.[215-221] In a series of studies from the Mayo Clinic, there was an increase of resistance to penicillin from 30%, noted in 1972, to over 70% in recent reports.[215,216,223] In the most recent study, reported in 1982, penicillin resistance among non-*fragilis Bacteroides* had risen strikingly, so that the MIC50 was 12.5 µg/mL and the MIC90 was 100 µg/mL.[216] In another investigation Brown and Waatti[224] found the MIC50 was 8.0 µg/mL for strains of *B melaninogenicus*. Similar results were reported by Heimdahl et al,[217] who found a MIC50 of 16.0 µg/mL for oral *Bacteroides* species isolated from saliva.

Resistance to penicillin in oral *Bacteroides* strains has been correlated with β-lactamase production.[215-217] There may be a higher incidence of β-lactamase–producing strains than reflected in the MIC, since production of this enzyme is often at a rather low level, not causing measurable resistance according to current criteria. The Mayo Clinic studies demonstrated a progressive increase in β-lactamase–producing *Bacteroides* strains, rising from 56% in 1977[215] to 80% in 1982.[216] Heimdahl et al[217] found that 95% of the oral *Bacteroides* strains produced β-lactamase, although many of these strains had extremely low levels of enzyme production. In isolates of *Bacteroides* from tonsils in children, Brook et al[219] found that 42% of these organisms produced β-lactamase. A subsequent publication by Brook[189] dealt with *Bacteroides* strains from abscesses of the head and neck of children; 30% of these isolates were β-lactamase producers.

Not only has resistance to penicillin been noted in bacteria isolated from orofacial infections, but clinical failures of this drug have also been reported. Cases of osteomyelitis of the mandible associated with resistant stains of *B melaninogenicus* failed on penicillin treatment, but subsequently responded to clindamycin.[225,226] In a report by Heimdahl et al[227] five patients with severe odontogenic infections had a poor clinical outcome with penicillin therapy due, according to the investigators, to the isolation of β-lactamase–producing *Bacteroides* strains. Brook[228] has also reported β-lactamase–producing organisms in children with orofacial and respiratory infections who failed penicillin treatment. In a disease involving similar pathogens, Levison et al[229] reported that patients with lung abscesses had a relatively poor outcome with penicillin therapy when compared to the results achieved with clindamycin.

There are three reports comparing different antibiotic therapies in odontogenic infections. Metronidazole and parenteral penicillin showed equal efficacy in acute dental infections.[230] The other study concerned prophylaxis against postoperative complications after surgical removal of impacted mandibular third molars.[231] The four antimicrobial agents, azidocillin, erythromycin, clindamycin, and doxycycline, showed equal efficacy, but the patients receiving antibiotics had a significantly better outcome than those receiving placebo. Our group has recently reported the results of the double-blind, prospective trial of penicillin and clindamycin in the treatment of 55 patients with moderate to severe odontogenic infections, and no differences were found in the treatment groups.[221]

Our results of penicillin resistance in anaerobic bacteria isolated from these infections are somewhat different from those noted by other investigators, as detailed above. Even using the National Committee for Clinical Laboratory Standards recommended low cutoff, equal to or greater than 1.0 µg/mL of penicillin,[22] which tends to exaggerate resistance levels, we encountered only 8.9% resistance to penicillin among all anaerobic isolates and 16% among the *B melaninogenicus* group. The resistance to clindamycin was also low, 1.9%; there were no resistant *Bacteroides* strains, but we did encounter two clindamycin-resistant strains of *Peptostreptococcus* and one resistant *Fusobacterium* strain.

## CONCLUSION

On the basis of our findings it would appear that resistance to penicillin can be quite variable among organisms isolated from infections associated with bacteria originating in the oral microflora. Despite the few reported cases of penicillin failure, the three trials involving penicillin showed no difference when it was compared with alternative antimicrobial drugs. These findings suggest that penicillin remains a useful treatment for infections with these organisms. It should be noted, however, that this recommendation would not apply in communities in which penicillin resistance runs rather high. In such circumstances, or in patients who are either allergic to penicillin or have failed previous treatment, clindamycin would be a satisfactory alternative.

# ROLE OF ANAEROBIC BACTERIA IN PERIODONTAL DISEASE

WALTER J. LOESCHE, DMD, PHD

## INTRODUCTION

Dental diseases such as dental decay and periodontal disease were estimated to cost the American public about $25 billion in 1987.[232] As such, the cost of dental treatment ranks as more expensive than the treatment of eye disease, diabetes, and arthritis, among others. The highly individualized, labor-intensive methods used to debride, repair, or replace the involved teeth account for the size of this expense. The treatment of periodontal disease, which is a major dental health problem in adults, is particularly labor-intensive. In the past 10 years, concepts and methods that were developed in caries research have provided insights into the causation and pathogenesis of periodontal disease. Foremost among these insights is the realization that many forms of periodontal disease are specific, albeit chronic, bacterial infections. The concepts of the specific plaque hypothesis that have been developed to explain the bacterial cause of dental decay[232-234] could also, with modifications, be applied to periodontal disease.

Microbial specificity in periodontal disease has taken longer to demonstrate, because prior to 1968 most investigators focused their attention on supragingival plaque, ie, plaque on the tooth surface above the gingival margin, and did not examine subgingival plaque, ie, plaque on the tooth surface below the gingival margin, as a separate microbial ecosystem. Also, the subgingival plaque flora comprises mainly anaerobic species, which can be cultured only when oxygen is rigorously eliminated from the atmosphere in which the bacterial colonies are isolated. Once these organisms were isolated, most of them could not be recognized as known species. The impact of this was not fully appreciated until it was reported in 1977 that about 60% of the bacteria cultured from diseased sites in patients with localized juvenile periodontitis were unidentifiable and were different from those found in healthy sites.[235] The possibility that this unusual clinical entity was due to one or more bacterial types that were unique to the disease situation caught the fancy of many persons and ushered in the age of microbial specificity in periodontal disease.

## ANAEROBIC NATURE OF PERIODONTAL INFECTIONS

*Plaque.* Several groups have examined the microbial flora in the subgingival plaques associated with various clinical entities, using a variety of approaches. Some investigators have examined the subgingival plaque directly, using phase-contrast and dark-field microscopy, and uniformly report the presence of large numbers and proportions of spirochetes.[236] However, because most spirochetes cannot be cultured, there have been few studies implicating any particular species in periodontal disease. The use of monoclonal and highly specific polyclonal antibodies to *Treponema denticola* has recently shown this species to be associated with adult forms of periodontitis.[237,238]

Other investigators have employed a quantitative continuous anaerobic technique to culture the subgingival plaque.[235,239-242] The plaque is removed from a discrete tooth site and is immediately placed into an anaerobic environment. The plaque is then disrupted by mechanical mixing or ultrasound, serially diluted, and plated on a variety of selective or nonselective media. This disruption increases the yield of viable organisms, but destroys the fragile spirochetal species.[243] It is not surprising, therefore, that these cultural studies implicate organisms other than spirochetes as being associated with periodontal disease. In fact, these cultural studies demonstrate such complexity in the bacterial flora that no single species predominates to the point of being considered responsible for the majority of the periodontal lesions.[239,240]

Instead of finding only one or two bacterial types that could be implicated in periodontal inflammation, workers have found as many as 10 species that could be associated with some form of periodontal disease (Table 28). Thus, the relationship between periodontal disease and specific microbes is more complicated than that observed between *Streptococcus mutans* or lactobacilli and dental caries.[232]

Collectively, these microscopic and cultural studies suggest that most forms of periodontitis may be related either to the overgrowth or to the presence of one or more bacterial types such as spirochetes,[236] especially *T denticola*,[236,237] black-pigmented *Bacteroides*, especially *Bacteroides gingivalis*,[241,242] nonpigmented *Bacteroides* such as *Bacteroides forsythus*,[240] and motile organisms such as *Wolinella* and *Selenomonas* sp[240,244] in subgingival plaques removed from discrete tooth surfaces. If one looks at this list of putative periodontal pathogens, a pattern can be discerned. All the organisms associated with adult periodontitis and early-onset periodontitis are anaerobes, whereas *Actinobacillus actinomycetemcomitans*, which is associated with the rarely encountered localized juvenile periodontitis, is a micro-

TABLE 28. BACTERIAL SPECIES IMPLICATED AS PATHOGENS IN PERIODONTAL DISEASE

| *Species* | *Gingivitis* | *Periodontitis* |
|---|---|---|
| Anaerobic | | |
| Spirochetes (unspeciated) | ANUG, SG | AP, EOP, RP |
| *Treponema denticola* | | AP, EOP, RP |
| *Bacteroides gingivalis* | | AP, EOP, PLA, RP |
| *Bacteroides forsythus* | | AP, EOP, PLA, JP |
| *Bacteroides intermedius* | ANUG, PG | AP, JP |
| *Fusobacterium nucleatum* | | AP |
| *Wolinella recta* | | EOP, PLA, JP |
| *Eubacterium* sp | | AP |
| Microaerophilic | | |
| *Actinobacillus actinomycetemcomitans* | | LJP |
| *Eikenella corrodens* | | EOP |
| Facultative or aerobic | | |
| *Pseudomonas* sp, *Escherichia coli* | | RP, PA |
| *Proteus*, other gram-negative bacilli | | SI |
| *Streptococcus faecalis* | | |
| *Candida* | | |

ANUG — acute necrotizing ulcerative gingivitis, SG — severe gingivitis, PG — pregnancy gingivitis, AP — adult periodontitis, EOP — early-onset periodontitis, RP — refractory periodontitis, PLA — progressive loss of attachment about single site, JP — juvenile periodontitis, LJP — localized juvenile periodontitis, PA — periodontal abscess, SI — suprainfections.

TABLE 29. DOUBLE-BLIND STUDIES INVOLVING METRONIDAZOLE

| *Reference* | *Selection Criteria* | *Treatment Groups* | *Treatment Modalities* | *Results* |
|---|---|---|---|---|
| Joyston-Bectal et al[246] | Clinical | Positive control | OHI, S, Chx, Pl | Test > positive control, significant |
| | | Test | OHI, S, Chx, Met | |
| Clark et al[247] | Clinical | Positive control | S, Pl | Test > positive control, not significant |
| | | Test | S, Met | |
| Lindhe et al[248] | Clinical | Half-mouth design | | |
| | | Control | S, RP | (Met, S, RP) > Met = (S, RP) > > > no Tx |
| | | | No Tx | |
| | | Test | S, RP, Met | |
| | | | Met | |
| Loesche et al[249] | Clinical, anaerobic infection | Positive control | Pl, S, RP | Test > positive control, significant reduction in probing and gain in attachment |
| | | Test | Met, S, RP | |
| Loesche et al[250] | Clinical, anaerobic infection | Positive control | Pl, S, RP | Test > positive control, significant reduction in surgical needs |
| | | Test | Met, S, RP | |
| Loesche et al[251] | Clinical, anaerobic infection | Positive control | Pl, S, RP | Test > positive control, significant reduction in in surgical needs |
| | | Test | Met, S, RP | |

OHI — oral hygiene instructions, S — scaling, Chx — topical chlorhexidine, Pl — placebo medication, Met — metronidazole, RP — root planing, Tx — therapy.

aerophilic organism. Aerobic and facultative organisms are occasionally associated with certain refractory forms of periodontitis and with periodontal abscesses. This pattern suggests that most forms of periodontal disease are anaerobic infections and might respond to an antimicrobial agent, such as metronidazole, whose spectrum of activity is limited to anaerobes.[245] But more important, if metronidazole is effective in the treatment of periodontal disease, this effectiveness would provide indirect evidence that periodontitis is an anaerobic infection. Thus, if metronidazole is successful in treating the clinical manifestations of periodontal disease, one might conclude that an anaerobic infection was occurring.

## TREATMENT OF ANAEROBIC PERIODONTAL INFECTIONS

Short-term usage of systemic metronidazole (1 to 4 weeks' duration) has been evaluated in six well-controlled studies in which the selection criteria for treatment were either clinical evidence of advanced disease or clinical evidence plus the diagnosis of an anaerobic infection associated with spirochetes (Table 29[246-251]). In the Joyston-Bectal et al double-blind study,[246] metronidazole caused a significantly greater reduction in probing depths about the teeth and an apparent gain in attachment of the teeth in patients with severe periodontitis compared to patients receiving a placebo. Both groups had received oral hygiene instructions, professional debriding of the teeth (scaling), and daily usage of a chlorhexidine gel, so that the only difference between the groups was in the metronidazole and placebo medications. The metronidazole had no effect upon supragingival plaque and gingival bleeding and was of no added value when the patients had a moderate periodontitis. These results were to be expected, because it is difficult to see how metronidazole could improve upon scaling, oral hygiene, and chlorhexidine in regard to supragingival plaque control. But in the deeper pockets, where scaling, oral hygiene, and chlorhexidine would be less effective because of reduced access to the plaque, the metronidazole conferred added benefits. This finding indicates that metronidazole is of value primarily in the treatment of subgingival infections and would not be indicated for supragingival plaque control, gingivitis, or moderate periodontitis.

A second double-blind metronidazole study was conducted in a small number of mentally retarded adolescents with moderate periodontal disease.[247] The patients' teeth were cleaned and scaled to the extent that was possible in these uncooperative subjects and then they were given 1 week of metronidazole or placebo. There was an apparent attachment gain in both treatment groups as measured in only one preselected disease site per patient, but the differences, while favoring metronidazole, were not significant. The lack of significance may reflect the small sample size and the moderate degree of periodontal disease, but it also may indicate that there is a need for rigorous debridement of the root surfaces for the optimization of the effect of any systemic antimicrobial agent.

This latter possibility was suggested by a clinical trial using a half-mouth design in which metronidazole or placebo was given in combination with rigorous debridement of only the teeth on one side of the mouth.[248] This half-mouth design, which is commonly used in dental studies, is thought to be an efficient design, as it provides additional treatment groups within any given number of patients. Hence, within a patient, all the teeth would be exposed to systemic placebo or metronidazole, but half the teeth would also be debrided, giving a total of four treatment modalities within two patient groups. The best results were obtained in the half-mouth receiving both debridement and metronidazole, whereas metronidazole alone or debridement alone yielded less impressive reductions in percentages of spirochetes and in numbers of sites with probing depths of $\geq 6$ mm. Clearly, the same dosage of metronidazole was more effective in the debrided pocket. This finding follows from the fact that in an undebrided pocket of 6 mm or more there may be about $10^8$ to $10^9$ bacteria, whereas in a debrided pocket there may be $10^4$ to $10^7$ residual bacteria. The levels of metronidazole in the crevicular fluid following use of 250-mg tablets taken three times daily is about 3 μg/mL.[252] This level is able to kill in vitro about $10^6$ to $10^7$ anaerobes per milliliter and should be an adequate drug level in a debrided pocket, but may not be adequate for an undebrided or minimally debrided root surface.

We have conducted three double-blind clinical trials of metronidazole in which we sought to determine the optimal time to integrate the metronidazole into the debridement and/or surgical treatments, and to evaluate the effect of metronidazole upon bacterial and clinical parameters, as well as any effects it might have upon the need for periodontal surgery. We selected patients on the basis of the diagnosis of an anaerobic subgingival infection, ie, spirochetes greater than 20% of the bacteria in the subgingival flora, and the need for periodontal surgery, and randomly assigned them to either the metronidazole or placebo group. The design was ethical in that all patients received the necessary debridement of the tooth surfaces. Thus, the group given the placebo medication was actually a positive control, as these patients received the normal periodontal therapy, while the test group received in addition to the normal therapy 1 week of systemic metronidazole (250 mg three times daily for 7 days).

In the first study,[249] the medication was initiated at the first of four to eight sessions in which root debridement was performed. The metronidazole treatment effect was greatest in those sites with greater initial morbidity, ie, probing depths of ≥6 mm. In those sites the probing depth decrease of 3.2 mm and the apparent attachment gain of 1.4 mm were significantly greater than the decrease of 1.6 mm in probing depth and the attachment gain of 0.2 mm observed in the placebo group. These results meant that the teeth had less periodontal inflammation and appeared to have more periodontal ligament attachment to the surrounding tissue. These clinical improvements correlated with a significant reduction in *B gingivalis* and spirochetes, suggesting that the healing was in response to the suppression of anaerobic infection in the subgingival plaque. Thus, we found that the metronidazole effect was greatest in the deeper pockets, and were able to associate this improvement with the suppression of certain members of the anaerobic flora.

In the second study[250] the identical protocol was followed and in addition the patients were evaluated for the need for periodontal surgery before and after root debridement and annually during the maintenance phase. The findings showed that 1 week of metronidazole, when superimposed upon debridement, significantly reduced the surgical needs by an average of 8.5 teeth per patient compared to an average of 3.0 teeth per patient in the placebo plus debridement group. All patients received the best debridement treatment our clinicians could provide; hence, the additional use of metronidazole resulted in about five fewer teeth per patient that needed periodontal surgery. This reduction had immediate cost and comfort benefits for the patient.

We had noted that debridement in the placebo group had reduced the load of spirochetes from about 11 million to about 3 million per pocket. This finding suggested that if the metronidazole had been given after debridement, it might have been more effective, as it would have had fewer spirochetes and other anaerobes to combat in the plaque. Thus, by repositioning the 1 week of metronidazole to the conclusion of the debridement, one might expect to see an improved clinical result. Accordingly, we initiated a third double-blind study[251] in which the metronidazole or placebo was given at the conclusion of the debridement procedures. The metronidazole patients currently are exhibiting a 60% reduction in teeth needing surgery compared to a 27% reduction in the placebo group. When all patients in the second and third studies are compared, the placement of the metronidazole at the completion of debridement is significantly better than placement at the start of the debridement procedures, in terms of reducing the surgical needs of the patient.

## SUMMARY

Microscopic examination and cultural studies of subgingival dental plaque have indicated that a complex, predominantly anaerobic flora is associated with periodontal disease. About 10 to 15 bacterial species, all of them anaerobic with the exception of *A actinomycetemcomitans*, have been suggested to be periodontal pathogens. These data indicate that most forms of periodontal disease are chronic anaerobic infections. This possibility has been evaluated by the systemic use of metronidazole, an antimicrobial whose spectrum of activity is limited to anaerobes.

These six metronidazole double-blind studies demonstrate that metronidazole, given for periods of time as short as 1 week, can lead to a significant improvement in periodontal health. Maximal benefits are obtained when the metronidazole is given after the tooth surfaces are debrided of plaque and calculus. The best response is often noted in the more advanced cases, in which an anaerobic flora including spirochetes and black-pigmented *Bacteroides* usually predominates in the subgingival plaque. The success of short-term metronidazole treatment in these investigations indicates that the overgrowth of certain anaerobes in the plaque is responsible for most forms of periodontal disease.

# ROLE OF ANAEROBIC BACTERIA IN POSTOPERATIVE WOUND INFECTIONS FOLLOWING ONCOLOGIC SURGERY OF THE HEAD AND NECK

JONAS T. JOHNSON, MD; VICTOR L. YU, MD

The surgical approach to tumors of the upper aerodigestive tract requires that the surgical procedure be undertaken in a contaminated environment. Even under ideal circumstances of optimal oral-dental hygiene, up to 1 million organisms per cubic centimeter of saliva can be present.

A diverse microbiologic population with a predominance of anaerobes is present in the oral cavity. Different anatomic sites have their own unique flora. For example, anaerobes and spirochetal forms localize to the gingival crevice, while streptococcal organisms predominate on surfaces of teeth. The aerobic microflora is composed primarily of streptococci, but also includes *Staphylococcus*, *Hemophilus*, and *Neisseria* species. For hospitalized patients, Enterobacteriaceae and enterococci are commonly found. Fungi, especially *Candida*, are often present, particularly in patients who have received antibacterial chemotherapy.

The need for perioperative prophylactic antibiotics has been confirmed in a number of placebo-controlled clinical trials (Table 30[253-259]). As a result, consensus exists among head and neck surgeons that antibiotic prophylaxis is mandatory for major oncologic head and neck surgical procedures. Prophylactic antibiotics should be administered prior to bacterial contamination; Burke[260] showed that when antibiotic administration was withheld within hours after contamination by the surgical procedure, wound infection rates were significantly higher.

With the proliferation of antimicrobial agents, the specific choice for prophylaxis in this setting has been somewhat contentious. We have conducted a series of prospective, randomized, double-blind clinical trials in an effort to examine the efficacy of specific antimicrobial agents as well as to assess the microbes most frequently implicated in postoperative wound infection following oncologic head and neck surgery.[258,261-263]

The study design was similar for all trials. Patients scheduled to undergo oncologic surgical procedures with expected contamination with oropharyngeal secretions (skin to mucous) were randomized into the various study regimens (Table 31). Patients undergoing transoral procedures or those in whom the skin was not closed were excluded. Patients were stratified according to a computer-generated code for potential cofactors of infection. These parameters included stage of disease (stage IV versus stage III or less), time of tracheotomy (antecedent tracheotomy versus concurrent tracheotomy), prior radiotherapy (no prior irradiation versus prior irradiation), closure technique (primary closure or split-thickness skin graft versus flap reconstruction), and procedure undertaken (laryngectomy versus other).

The antibiotics were administered to the patient intravenously 1 to 2 hours prior to operation. Subsequent antibiotic administration was continued intravenously every 8 hours for a total of four doses. All patients were followed up postoperatively until discharged from the hospital and then at monthly intervals for the first postoperative year.

A total of 37 postoperative wound infections were documented in these eight clinical trials (Table 31). Wound infection was evidenced by either the development of a purulent collection or breakdown of the wound with presence of a mucocutaneous fistula. These occurrences were seen in relatively equal frequencies. The onset of the postoperative wound infection usually occurred after 5 days, with a mean of 10 postoperative days. In 6 patients, wound infection developed early and could theoretically have been preventable by antibiotic prophylaxis. The severity of the postoperative wound infection did not correlate with the antibiotic administered. The average hospitalization of the 354 patients studied was 14 days when healing occurred without postoperative wound infection. The development of a postoperative wound infection delayed discharge from the hospital an average of 10 days per patient.

Infection developed in 33% (7/21) of those receiving cefazolin at a dose of 500 mg — an incidence of postoperative wound infection considered to be excessive (Table 31).[261] High-dose cefazolin[262] (2 g), moxalactam,[262] cefotaxime, cefoperazone,[258] the combination of clindamycin-gentamicin,[261,263] and clindamycin[263] alone were observed to have more acceptable rates of infection.

Ninety-two percent of the infections were polymicrobial ones in which gram-positive aerobic bacteria, gram-negative aerobic bacteria, and anaerobic bacteria were isolated. Aerobic gram-negative rods were identified in 73% (27/37) of wound infections (Table 32). Aerobic gram-positive cocci were encountered in 89% (33/37), with streptococcal species being the most frequently isolated or-

TABLE 30. INCIDENCE OF INFECTION IN PATIENTS UNDERGOING ONCOLOGIC SURGERY OF HEAD AND NECK RECEIVING PLACEBO

| *Author* | *Infection Rate* |
|---|---|
| Piccart et al[253] | 28% |
| Dor and Klastersky[254] | 36% |
| Seagle et al[255] | 48% |
| Eschelman et al[256] | 50% |
| Ketchum et al[257] | 65% |
| Johnson et al[258] | 78% |
| Becker and Parell[259] | 87% |

TABLE 31. INCIDENCE OF INFECTION IN PATIENTS UNDERGOING ONCOLOGIC SURGERY OF HEAD AND NECK ACCORDING TO ANTIBIOTIC REGIMEN EMPLOYED

| *Antibiotic* | *Patients Studied* | *Infections* | *Rate (%)* |
|---|---|---|---|
| Placebo | 9 | 7 | 78 |
| Cefazolin, 500 mg | 21 | 7 | 33 |
| Cefazolin, 2 g | 59 | 5 | 8.5 |
| Cefotaxime | 48 | 4 | 8 |
| Cefoperazone | 55 | 6 | 11 |
| Moxalactam | 59 | 2 | 3.4 |
| Clindamycin | 52 | 2 | 3.8 |
| Clindamycin-gentamicin | 81 | 4 | 4.9 |

TABLE 32. AEROBIC BACTERIA ISOLATED FROM 37 PATIENTS UNDERGOING ONCOLOGIC SURGERY OF HEAD AND NECK WITH DOCUMENTED WOUND INFECTIONS

| | *Placebo* | | | | | | | *Cefazolin (500 mg)* | | | | | | | *Gent and CL* | | | | *Cefoperazone* | | | | | | *Cefotax-ime* | | | | *Cefazolin (2 g)* | | | | | *MX* | | *CL* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* | *10* | *11* | *12* | *13* | *14* | *15* | *16* | *17* | *18* | *19* | *20* | *21* | *22* | *23* | *24* | *25* | *26* | *27* | *28* | *29* | *30* | *31* | *32* | *33* | *34* | *35* | *36* | *37* |
| Gram-positive | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| β-Hemolytic *Streptococcus* (not group A) | | | | | | X | X | | | | | X | | | | | | | | X | X | X | | | | | | | | | | | | | | | |
| *Streptococcus intermedius* | | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *Streptococcus viridans* | X | | | X | | X | X | | X | | | | | | X | X | X | X | | X | X | X | | | | X | X | X | | | | X | X | X | X | X | |
| *Streptococcus faecalis* | | | | | | | | | | X | | X | | X | X | | | | | X | | | | | | | | | | | | | | | | | |
| Nonhemolytic *Streptococcus* | | | | | X | | | | X | | | | | | | | | | X | | X | | | | | | | | | | | | | | | | |
| Microaerophilic *Streptococcus* | | X | | | X | X | | | | X | X | | | X | | | | | X | | | X | | | X | | | | | | X | | X | X | | | |
| *Staphylococcus aureus* | X | | | X | | | | X | | | | | | | | | X | | | | X | | | | X | | X | | X | | | | | | | | |
| *Staphylococcus epidermidis* | | | | | | | X | | X | | | | | | | X | | | X | X | | | | | | | | | | | | | | X | | | X |
| *Bacillus* species | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | | | |
| *Neisseria flava* | | | | | | | | | | | | | | | X | | X | | X | | X | X | | | | | | X | | | | X | | | X | X | |
| Gram-negative | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *Escherichia coli* | | | | | | | | X | | | | | | | X | | | | | | | X | | | | | X | | | | | | | X | | | |
| *Enterobacter aerogenes* | | | | | | | | | | X | | | | | X | | | | | X | | | | | | | | | | | | | | X | | | |
| *Enterobacter cloacae* | | | | | | | | | | | | | | | X | | | | | X | | | X | X | | | X | | | | | X | | | | | |
| *Enterobacter agglomerans* | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | |
| *Proteus mirabilis* | | | | X | | | | | X | | | X | | | | | X | | | | | | | | | | | | | | | | | X | | | |
| *Morganella morganii* | | | | | | | | | | | | | | X | | | | | | | | | | | | | | | | | | | | | | | |
| *Kingella kingae* | | | | | | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | | | |
| *Pseudomonas aeruginosa* | | | | | | | | | | | | | | | X | X | | | X | | | | X | | | | | | X | | | | | | | | |
| *Pseudomonas maltophilia* | | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | | | | | | | |
| *Klebsiella* species | | | | | | | | | | | | | | | X | | | | | X | | | | | | | X | | | | | | | | X | | X |
| *Serratia marcescens* | | | | | | | | X | | | | | | | | | | | | X | X | X | | | | | | | | X | | | | X | | | X |
| *Hemophilus aphrophilus* | | | | | | X | X | | | | | | | | | | | | | | X | | | | | | | | | | | | | | | | |
| *Citrobacter diversus* | | | | | | | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | | |
| *Acinetobacter* species | | | | | | X | | | | | | | | X | | | | | | | X | | | X | | X | X | | | | | | | X | | | |
| *Eikenella corrodens* | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | | | | | | | | |

Gent — gentamicin, CL — clindamycin, MX — moxalactam.

TABLE 33. ANAEROBIC BACTERIA ISOLATED FROM 37 PATIENTS UNDERGOING ONCOLOGIC SURGERY OF HEAD AND NECK WITH DOCUMENTED WOUND INFECTIONS

| | *Placebo* | | | | | | | *Cefazolin (500 mg)* | | | | | | | *Gent and CL* | | | | *Cefoperazone* | | | | | | *Cefotax-ime* | | | | *Cefazolin (2 g)* | | | | | *MX* | | *CL* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* | *10* | *11* | *12* | *13* | *14* | *15* | *16* | *17* | *18* | *19* | *20* | *21* | *22* | *23* | *24* | *25* | *26* | *27* | *28* | *29* | *30* | *31* | *32* | *33* | *34* | *35* | *36* | *37* |
| Gram-positive | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *Peptostreptococcus micros* | | | | | | | | | | | | | | | | | | | | | X | | | | X | | | X | | | | | | | | | |
| *Propionibacterium* species | | | | | | X | | | | | | | | | | | | | X | X | | | | | | X | | | X | X | | | | | | | |
| *Lactobacillus* species | | | | | | | | | | | | | | | | | | X | | | | | | | | | | | | | | | | | | | X |
| Gram-negative | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *Bacteroides* species | | | | | | | | | | | | | | | | | | | | X | X | X | | X | X | | | | | | | X | | | | | |
| *Bacteroides oralis* | | | | | | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | | | |
| *Bacteroides melaninogenicus* | | | X | | | | | | | | X | | | X | | | X | | X | X | | | | X | | | | X | | X | | X | X | | | | |
| *Bacteroides asaccharolyticus* | | | X | | | | | | | | X | | | X | | | X | | X | X | | | | X | | | | X | | X | | X | X | | | | |
| *Bacteroides fragilis* | | | | | | | | | | | | | X | X | | | | | | | | | | | | | | | | X | | | | X | | | |
| *Bacteroides fragilis (vulgaris)* | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | | | | X | | | | |
| *Veillonella* species | | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | | | | | | | |

Gent — gentamicin, CL — clindamycin, MX — moxalactam.

TABLE 34. FUNGI ISOLATED FROM 37 PATIENTS WITH DOCUMENTED WOUND INFECTIONS

| | *Placebo* | | | | | | | *Cefazolin (500 mg)* | | | | | | | *Gent and CL* | | | | *Cefoperazone* | | | | | | *Cefotaxime* | | | | *Cefazolin (2 g)* | | | | | *MX* | | *CL* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* | *10* | *11* | *12* | *13* | *14* | *15* | *16* | *17* | *18* | *19* | *20* | *21* | *22* | *23* | *24* | *25* | *26* | *27* | *28* | *29* | *30* | *31* | *32* | *33* | *34* | *35* | *36* | *37* |
| *Candida albicans* | X | | | | | | | | | | | X | | | X | | X | | X | | | | | | X | | | | | | | | | | | | |
| *Candida krusei* | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | |
| *Candida stellatoidea* | | | | | | | | | X | | | | | | | X | | | | | | | | | | | | | | | | | | | | X | |
| *Candida tropicalis* | | | | | | | | | | | | | | | | | | X | | X | | X | | | | X | | | | | | | | | | | X |
| *Candida parapsilosis* | | | | | | | | | | | | | | | | | X | | | | | | | | | | | | | | | | | | | | |

Gent — gentamicin, CL — clindamycin, MX — moxalactam.

ganisms.

Anaerobic cultures were positive in 57% (21/37; Table 33). Usually, multiple anaerobic bacteria were isolated, with *Bacteroides* species frequently encountered. Three patients had bacteremia in which anaerobic bacteria (*Propionibacterium acnes, Bacteroides asaccharolyticus*, and microaerophilic streptococci) were isolated from blood and wound concomitantly. It should be noted that these anaerobic bacteria are part of the commensal microflora of the oral cavity.

Resistance of the organisms isolated from the infected wounds to the prophylactic antibiotic administered was never documented.

*Candida* species were isolated from 38% (14/37) of patients. None of these patients received specific antifungal therapy, and all wound infections resolved with the combination of surgical incision and drainage and antibacterial agent administration. On this basis, we conclude that fungi are more likely colonizing flora, rather than pathogens (Table 34).

From a theoretic standpoint, the organisms most likely to be implicated in wound infection would be those organisms that are normal commensal microflora of the site of surgery. In the oral cavity, with its high population of anaerobic bacteria, these same bacteria could likely be pathogenic following head and neck operations. On the other hand, cultures taken from wounds considered to be infected by clinical criteria reveal a wide variety of bacteria, including the frequent isolation of aerobic gram-negative rods, which are generally not part of the normal flora of the oral cavity.[264]

In order to directly address the issue of the role of anaerobic and aerobic commensal microflora versus that of aerobic gram-negative rods, we conducted a clinical trial in which clindamycin versus clindamycin combined with gentamicin was administered in a prospective, double-blind trial.[263] The spectrum of clindamycin includes aerobic and anaerobic microflora of the oral cavity, but does not include aerobic gram-negative rods. Despite the omission of gram-negative coverage in the clindamycin-only group, the incidence of wound infection was identical in both groups. Thus, the presence of aerobic gram-negative rods more likely represents colonization rather than pathogenicity for most patients. Similar conclusions were drawn from a trial of 80 patients randomized to clindamycin alone versus clindamycin plus netilmicin.[253]

We speculate that wound infection develops through separation of the pharyngeal (interior) suture line with resultant persistent soiling of the deep tissues of the neck. Support for this thesis was given by Newman et al,[265] who demonstrated that salivary contrast medium (technetium 99) could be localized to the deep tissues of the neck days after operation, but prior to the development of clinically apparent wound infections. It is important to note that prolonged administration of antibiotics fails to prevent infection in the setting of persisting salivary contamination.

In summary, we conclude that oropharyngeal aerobic and anaerobic bacteria are primary pathogens for postoperative infections of the head and neck.

# SUMMARY AND CONCLUSIONS

## ROLE OF ANAEROBIC BACTERIA IN INFECTIONS OF THE UPPER RESPIRATORY TRACT AND HEAD AND NECK

JEROME O. KLEIN, MD

Recent improvements in techniques for isolation and identification of the various genera and species of anaerobic bacteria have provided a better understanding of the anaerobic flora of humans and their role in disease. Anaerobes are present on the skin, in the mouth, in the intestines, and in the genital tract. Because they are so prevalent and abundant at these sites, the distinction between colonization (presence of the organism without clinical signs or symptoms) and disease (presence of the organism with clinical signs or symptoms) has often been indistinct. The technical features of isolation of anaerobic bacteria need to be understood by both the investigator and clinician: materials have to be obtained from the site of infection by using techniques that limit contamination from colonizing organisms on skin and mucosal surfaces; materials must be transported to the laboratory without loss of viability; and materials must be inoculated on or in appropriate media placed in optimal atmospheres. Because anaerobic bacteria have varying susceptibility to available antimicrobial agents, the physician should be aware of those infections of the upper respiratory tract and head and neck in which anaerobes may play major roles and of the susceptibility pattern for the anaerobic species.

The Workshop brought together major investigators of the microbiology and clinical features of anaerobic infections. Although the discussion as reflected in these proceedings indicates that there is still controversy about the role of anaerobic bacteria in specific diseases, there was common ground that provides a basis for understanding optimal management of the patient with presumed or documented anaerobic infection. The Workshop held in December 1988 may serve as a point in time to judge subsequent advances in anaerobic bacteriology and infections of the head and neck and upper respiratory tract.

### ANAEROBIC BACTERIA AND DISEASES

Anaerobes have been implicated as causative agents in acute and chronic otitis media, acute and chronic sinusitis, intracranial complications of chronic otitis and sinusitis, tonsillar and retropharyngeal abscesses, recurrent tonsillitis, suppurative thyroiditis, and parotitis. As discussed at this conference, anaerobic bacteria have an incontrovertible role only in odontogenic infections, soft tissue infections of the head and neck, chronic otitis and sinusitis, and complications such as brain abscess arising from these sites. The role of anaerobic bacteria is discussed for each of these diseases by the authors in these proceedings. A summary list that provides a consensus of the role of anaerobic bacteria in the various diseases of the head and neck and upper respiratory tract is provided in Table 35.

Anaerobes that predominate in importance in infections of the head and neck are *Bacteroides* species (*Bacteroides melaninogenicus, Bacteroides oralis, Bacteroides fragilis*), *Peptostreptococcus* sp, and *Fusobacterium* sp. *Actinomyces* species are of concern in odontogenic infections. Less frequently, *Propionibacterium* sp and *Clostridium* sp may play a role in suppurative infections.

Anaerobic bacteria are often present with other organisms at the site of infection. The polymicrobial nature of these infections makes it even more difficult to assign specific roles to individual bacteria. Do they play primary or secondary roles, or no role at all in the infectious disease? Do they increase virulence of other bacteria? Do they shield bacteria that are susceptible to penicillin by producing $\beta$-lactamase? These and other questions about the pathogenic role of anaerobic bacteria are still subjects of active investigation.

### TECHNIQUES FOR PROCESSING MATERIALS FOR ANAEROBIC BACTERIA

The physician should consult with the microbiologist to obtain guidance in optimal techniques for obtaining and transporting specimens to the laboratory for isolation and identification. Doctor Finegold provided suggestions for processing materials from various sites and for asking appropriate questions of the microbiologist. Most important is sterilization of the surface of the area so that the prevalent anaerobic flora on skin and mucosal surfaces will not confuse results obtained from the site of disease. Aspiration from the site of infection with a syringe and needle or tissue biopsy is optimal. Swabs are the least satisfactory for obtaining materials for accurate diagnosis of anaerobic bacteria. Gram stains provide important information

TABLE 35. ROLE OF ANAEROBIC BACTERIA IN INFECTIONS OF UPPER RESPIRATORY TRACT, HEAD, AND NECK

| *Disease* | *Role of Anaerobic Bacteria* |
|---|---|
| Otitis media | |
| Acute | Minor |
| Chronic | Minor |
| Intracranial complications | Minor |
| Sinusitis | |
| Acute | Minor |
| Chronic | Major |
| Intracranial complications | Major |
| Pharyngotonsillitis | |
| Acute | Rare or none |
| Chronic | Minor |
| Peritonsillar abscess | Major |
| Odontogenic infections | |
| Endodontal | Major |
| Periodontal | Major |
| Parapharyngeal disease | |
| Space infections | Major |

Minor — anaerobic bacteria should be considered in presumptive therapy only if disease is severe or life-threatening, Major — anaerobic bacteria should be considered in presumptive therapy, Rare or none — anaerobic bacteria need not be considered in presumptive therapy.

TABLE 36. ANTIBIOTIC SUSCEPTIBILITY OF MAJOR ANAEROBIC BACTERIA RESPONSIBLE FOR INFECTIONS OF UPPER RESPIRATORY TRACT, HEAD, AND NECK (PERCENTAGES OF STRAINS SUSCEPTIBLE)

| *Antibiotic* | Peptostreptococcus | Propionibacterium | Clostridium | Fusobacterium | Actinomyces | Bacteroides fragilis | *No Genus* |
|---|---|---|---|---|---|---|---|
| Penicillin G | >90 | >90 | 50 to 90 | 70 to 90 | >90 | <50 to 70 | >50 to 70 |
| Antipseudomonal penicillins | >90 | >90 | >90 | >90 | >90 | 70 to >90 | 50 to >90 |
| Cefoxitin | >90 | >90 | <50 to 90 | 70 to >90 | 70 to 90 | 70 to 90 | >90 |
| Imipenem-cilastatin | >90 | >90 | >90 | 70 to 90 | >90 | >90 | >90 |
| Combined penicillin and $\beta$-lactamase inhibitor (amoxicillin-clavulanate) | >90 | >90 | >90 | >90 | >90 | >90 | >90 |
| Clindamycin | >90 | >90 | 70 to 90 | >90 | >90 | 70 to >90 | >90 |
| Chloramphenicol | >90 | >90 | >90 | >90 | >90 | >90 | >90 |
| Metronidazole | 70 to >90 | <50 | >90 | >90 | <50 | >90 | >90 |

Modified from Styrt B, Gorbach SL. Recent developments in the understanding of the pathogenesis and treatment of anaerobic infections. N Engl J Med 1989;321:298-302.

about the quantitation of the various morphologic types of bacteria.

## SUSCEPTIBILITY TO ANTIMICROBIAL AGENTS

Thornsberry noted that there are still technical problems associated with susceptibility tests for anaerobic bacteria performed in clinical microbiology laboratories. For the most part, susceptibility tests should be considered for investigational purposes. If the patient has failed to respond to antimicrobial therapy and has severe and life-threatening illness that is likely due to anaerobic bacteria, consultation with a laboratory expert in anerobic bacteriology would be of value in providing precise data on susceptibility.

Initial therapy of diseases of the head and neck and upper respiratory tract may need to include antimicrobial agents effective against anaerobic bacteria. Penicillin G is effective for all but the $\beta$-lactamase–producing *Bacteroides* species. Antipseudomonal penicillins and combinations of a penicillin plus a $\beta$-lactamase inhibitor provide more complete coverage. The spectrum of activity of these penicillins and other drugs of value for anaerobic bacteria is provided in Table 36.

## STRATEGY OF MANAGEMENT

The consensus of the authors about the strategy of management for the patient with a head and neck and upper respiratory tract infection that may include anaerobic bacteria was similar to strategies for other infectious diseases: obtain materials for culture by using optimal techniques, consider the likely pathogens, including anaerobic bacteria, that may cause disease at the site of infection (Table 35), select an initial antimicrobial regimen that will provide activity against the likely pathogens (Table 36), and be guided by the results of cultures to provide continuing treatment.

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